

(19)

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 1 110 957 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
27.06.2001 Bulletin 2001/26

(51) Int Cl.7: C07D 277/64, C07D 263/56,
C07D 235/16, C07D 417/06,
C07D 417/14, C07D 413/06,
C07D 403/06, A61K 31/4184,
A61K 31/428, A61K 31/423,
A61P 25/00

(21) Application number: 99811207.2

(22) Date of filing: 24.12.1999

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE

Designated Extension States:
AL LT LV MK RO SI

(71) Applicant: Applied Research Systems ARS
Holding N.V.
Curacao (AN)

(72) Inventors:
• Halazy, Serge
74100 Vétraz-Monthoux (FR)

- Church, Dennis
1291 Commugny (FR)
- Camps, Montserrat
1290 Versoix (CH)
- Gaillard, Pascale
74160 St. Julien-en-Genevois (FR)
- Gotteland, Jean-Pierre
74160 Beaumont (FR)

(74) Representative: Hassa, Jürgen
Serono International S.A.,
12, Chemin des Aulx
1228 Plan-les-Ouates (CH)

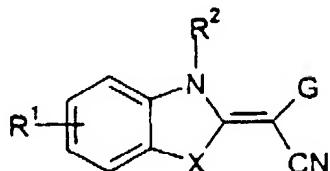
(54) Benzazole derivatives and their use as JNK modulators

(57) The present invention is related to benzazole derivatives according to formula I

X is O, S or NR⁰,

G is selected from the group comprising or consisting of unsubstituted or substituted aryl or heteroaryl substituents, unsubstituted or substituted 3-8-membered saturated or unsaturated ring systems containing at least one heteroatom selected from N, O or S; said 3-8-membered ring system may be fused with a substituted or unsubstituted aryl or heteroaryl system thus providing a bicyclic system;

notably for use as pharmaceutically active compounds. Said benzazole derivatives are efficient modulators of the JNK pathway, they are in particular efficient and selective Inhibitors of JNK2 and/or 3. The present invention is furthermore related to certain novel benzazole derivatives of formula I.



I

wherein

EP 1 110 957 A1

Description**Field of the Invention**

5 [0001] The present invention is related to benzazole derivatives and its tautomers for use as pharmaceutically active compounds, as well as pharmaceutical formulations containing such benzazole derivatives. In particular, the present invention is related to benzazole derivatives displaying a substantial modulatory, notably an inhibitory activity of the JNK (Jun-Kinase) pathway and which are therefore particularly useful in the treatment of disorders of the autoimmune and the neuronal system. The present invention is furthermore related to novel benzazole derivatives as well as to
10 methods of their preparation.

Background of the invention

15 [0002] Apoptosis denotes the complex contortions of the membrane and organelles of a cell as it undergoes the process of programmed cell death. During said process, the cell activates an intrinsic suicide program and systematically destroys itself. The following series of events can be observed :

- 20 • The cell surface begins to bleb and expresses pro-phagocytic signals. The whole apoptotic cell then fragments into membrane-bound vesicles that are rapidly and neatly disposed of by phagocytosis, so that there is minimal damage to the surrounding tissue.
- The cell then separates from its neighbours.

25 [0003] The nucleus also goes through a characteristic pattern of morphological changes as it commits genetic suicide, the chromatin condenses and is specifically cleaved to fragments of DNA.

30 [0004] Neuronal cell death plays an important role in ensuring that the nervous system develops normally. It appears that the death of developing neurones depends on the size of the target that they innervate: cells with fewer synaptic partners are more likely to die than those that have formed multiple synapses. This may reflect a process, which balances the relative number of pre- to post-synaptic neurones in the developing nervous system. Although neuronal cell death was assumed to be apoptotic, it was only recently that neurones in developing rodent brain were conclusively shown to undergo apoptosis as classified by morphology and DNA fragmentation. As cell death during development is clearly not a pathological process, it makes sense that cells actually cease to exist.

35 [0005] Neuronal death occurs via either apoptotic or necrotic processes following traumatic nerve injury or during neurodegenerative diseases. Multiple components are emerging as key players having a role in driving neuronal programmed cell death. Amongst the components leading to neuronal apoptosis are members of the SAPK/JNK being a subfamily of MAP Kinases (MAPKs).

40 [0006] MAPKs (mitogen-activated protein kinases) are serine/threonine kinases that are activated by dual phosphorylation on threonine and tyrosine residues. In mammalian cells, there are at least three separate but parallel pathways that convey information generated by extracellular stimuli to the MAPKs. Said pathways consist of kinase cascades leading to activation of the ERKs (extracellular regulated kinases), the JNKs (c-Jun N-terminal kinases), and the p38/CSBP kinases. While both the JNK and p38 pathways are involved in relaying stress-type extramolecular signals, the ERK pathway is primarily responsible for transducing mitogenic/differentiation signals to the cell nucleus.

45 [0007] SAPK cascades represent a sub-family of the mitogen-activating protein kinase family, that are activated by different external stimuli including DNA damage following UV irradiation, TNF- α , IL-1 β , ceramide, cellular stress, and reactive oxygen species and have distinct substrate specificities. Signal transduction via MKK4/JNK or MKK3/p38 results in the phosphorylation of inducible transcription factors, c-Jun and ATF2, which then act as either homodimers or heterodimers to initiate transcription of down-stream effectors.

50 [0008] c-Jun is a protein that is forming homodimers and heterodimers (with e.g. c-Fos) to produce the transactivating complex AP-1 which is required for the activation of many genes (e.g. matrix metalloproteinases) involved in the inflammatory response. The JNKs were discovered when it was found that several different stimuli such as UV light and TNF- α stimulated phosphorylation of c-Jun on specific serine residues in the N-terminus of the protein.

55 [0009] In a recent publication of Xie X et al, (*Structure* 1998, 6 (8); 983-991) it has been suggested that activation of stress-activated signal transduction pathways are required for neuronal apoptosis induced by NGF withdrawal in rat PC-12 and superior cervical ganglia (SCG) sympathetic neuronal cells. Inhibition of specific kinases, namely MAP kinase kinase 3 (MKK3) and MAP kinase kinase 4 (MKK4), or c-Jun (part of the MKK4 cascade) may be sufficient to block apoptosis (see also Kumagae Y et al, in *Brain Res Mol Brain Res*, 1999, 67(1), 10-17 and Yang DD et al in *Nature*, 1997, 389 (6653); 865-870). Within a few hours of NGF deprivation in SCG neurones, c-Jun becomes highly phosphorylated and protein levels increase. Similarly in rat PC-12 cells deprived of NGF, JNK and p38 undergo sus-

tained activation while ERKs are inhibited. Consistent with this JNK3 KO mice are resistant to excitotoxicity induced apoptosis in the hippocampus and more importantly they display greatly reduced epileptic like seizures in response to excitotoxicity as compared to normal animals (*Nature* 1997, 389, 865-870).

[0010] More recently, it has been reported that the JNK signalling pathway is implicated in cell proliferation and could play an important role in autoimmune diseases (*Immunity*, 1998, 9, 575-585; *Current Biology*, 1999, 3, 116-125) which are mediated by T-cell activation and proliferation.

[0011] Naive (precursor) CD4⁺ helper T (Th) cells recognise specific MHC-peptide complexes on antigen-presenting cells (APC) via the T-cell receptor (TCR) complex. In addition to the TCT-mediated signal, a costimulatory signal is provided at least partially by the ligation of CD28 expressed on T-cells with B7 proteins on APC. The combination of these two signals induces T-cell clonal expression.

[0012] After 4-5 days of proliferation, precursor of CD4⁺ T cells differentiate into armed effector Th cells that mediate the functions of the immune system. During the differentiation process, substantial reprogramming of gene expression occurs.

[0013] Two subsets of effector Th cells have been defined on the basis of their distinct cytokine secretion pattern and their immunomodulatory effects: Th1 cells produce IFNy and LT (TNF- β), which are required for cell-mediated inflammatory reactions; Th2 cells secrete IL-4, IL-5, IL-6, IL-10 and IL-13, which mediate B cell activation and differentiation. These cells play a central role in the immune response. The JNK MAP Kinase pathway is induced in Th1 but not in Th2 effector cells upon antigen stimulation. Furthermore, the differentiation of precursor CD4⁺ T cells into effector Th1 but not Th2 cells is impaired in JNK2-deficient mice. Therefore, in recent years it has been realized that the JNK kinase pathway plays an important role in the balance of Th1 and Th2 immune response through JNK2.

[0014] With the objective of inhibiting the JNK kinase pathway, WO/9849188 teaches the use of a human polypeptide, i.e. JNK-interacting protein 1 (JIP-1), which is a biological product and which has also been assayed for overcoming apoptosis related disorders.

[0015] Although such human polypeptides have been confirmed to have an inhibitory effect onto the JNK kinase pathway, a whole variety of drawbacks are associated with their use:

- Active bio-peptides or bio-proteins are only obtained by means of rather comprehensive and expensive bio-synthesis which consequently frequently renders the resulting products fairly cost-intensive.
- The peptides are known to display poor membrane penetration and may not cross the blood brain membrane,
- Furthermore, their bio-availability is usually rather restricted as notably the oral administration is not available because of decomposition through hydrolysis of said peptides within the acid medium of the stomach, their half-life is substantially restricted by digestion for instance due to the intestinal presence of proteases and, finally,
- In view of the crucial tolerance of administered products, it is a general concern that bio-peptides or bio-proteins are frequently viewed by the host body as intruding material to be disposed of, thus setting off an anti-body response.

[0016] Hence, it was an objective of the present invention to provide relatively small molecules that avoid essentially all of the above-mentioned drawbacks arising from the use of bio-peptides or bio-proteins, however, which are suitable for the treatment of a variety of diseases, in particular of neuronal or the autoimmune system related disorders. It was notably an objective of the present invention to provide relatively small molecule chemical compounds being able to modulate, preferably to down-regulate or to inhibit the JNK (Jun kinase) pathway so to be available as a convenient method of treating a host of diseases. Moreover, it was an objective of the present invention to provide methods for preparing said small molecule chemical compounds. It was furthermore an objective of the present invention to provide a new category of pharmaceutical formulations for the treatment of a host of diseases. It was finally an objective of the present invention to provide a method of treating diseases that are caused by disorders of the autoimmune and/or the neuronal system.

Description of the Invention

[0017] The aforementioned objectives have been met according to the independent claims. Preferred embodiments are set out within the dependent claims which are incorporated herewith.

[0018] The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader definition.

[0019] "C₁-C₆-alkyl" refers to monovalent alkyl groups having 1 to 6 carbon atoms. This term is exemplified by groups

such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-hexyl and the like.

[0020] "Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g. phenyl) or multiple condensed rings (e.g. naphthyl). Preferred aryl include phenyl, naphthyl and the like.

[0021] "Heteroaryl" refers to a monocyclic heteroaromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group.

5 Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, Isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isolindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinolizinyl, quinazolinyl, phthalazinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl or benzoquinolyl.

10 [0022] "Alkenyl" refers to alkenyl groups preferable having from 2 to 6 carbon atoms and having at least 1 or 2 sites of alkenyl unsaturation. Preferable alkenyl groups include ethenyl (-CH=CH₂), n-propenyl (-CH₂CH=CH₂) and the like.

15 [0023] "Alkynyl" refers to alkynyl groups preferably having 2 to 6 carbon atoms and having at least 1-2 sites of alkynyl unsaturation, preferred alkynyl groups include ethynyl (-C≡CH), propargyl (-CH₂C≡CH), and the like.

[0024] "Acetoxy" refers to the group -OC(O)R where R includes C₁-C₆-alkyl, aryl or heteroaryl.

[0025] "Alkoxy" refers to the group "C₁-C₆-alkyl-O-" or "-O-aryl" or "O-heteroaryl". Preferred alkoxy groups include by way of example, methoxy, ethoxy, phenoxy and the like.

20 [0026] "Alkoxy carbonyl" refers to the group -C(O)OR where R includes "C₁-C₆-alkyl" or "aryl" or "heteroaryl".

[0027] "Aminocarbonyl" refers to the group -C(O)NRR' where each R, R' includes independently hydrogen or C₁-C₆-alkyl or aryl or heteroaryl.

[0028] "Aminoacyl" refers to the group -NR(CO)R' where each R, R' is independently hydrogen or C₁-C₆-alkyl or aryl or heteroaryl.

25 [0029] "Halogen" refers to fluoro, chloro, bromo and iodo atoms.

[0030] "Sulfonyl" refers to group "R-SO₂" wherein R is selected from H, aryl, heteroaryl, C₁-C₆-alkyl, C₁-C₆-alkyl substituted with halogens e.g. a CF₃-SO₂ group.

[0031] "Sulfoxyl" refers to a group "R-S(=O)-" wherein R is selected from H, C₁-C₆-alkyl, C₁-C₆-alkyl substituted with halogens e.g. a CF₃-SO- group, aryl, heteroaryl.

30 [0032] "Thioalkoxy" refers to groups "C₁-C₆-alkyl-S-", or "aryl-S-" or "heteroaryl-S-". Preferred thioalkoxy groups include thiomethoxy, thioethoxy, and the like.

[0033] "Substituted or unsubstituted": Unless otherwise constrained by the definition of the individual substituent, the above set out groups, like alkyl, heteroaryl, alkenyl, alkynyl and aryl etc. groups can optionally be substituted with from 1 to 5 substituents selected from group consisting of C₁-C₆-alkyl, acetoxy, alkoxy, alkenyl, alkynyl, amino, aminoacyl, aminocarbonyl, alkoxy carbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxyl, sulfoxy, thioalkoxy, trihalomethyl and the like.

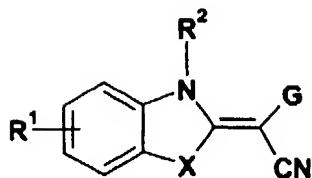
35 [0034] "Pharmaceutically acceptable salts or complexes" refers to salts or complexes that retain the desired biological activity of the below-identified compounds of formula I and exhibit minor or no undesired toxicological effects. Examples of such salts include, but are not restricted to acid addition salts formed with inorganic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene sulfonic acid, naphthalene disulfonic acid, and polygalacturonic acid. Said compounds can also be administered as pharmaceutically acceptable quaternary salts known by a person skilled in the art, which specifically include the quarternary ammonium salt of the formula -NR₂R', R'' + Z⁻, wherein R, R', R'' is independently hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, fumarate, citrate, tartrate, ascorbate, cinnamate, mandelate, and diphenylacetate).

40 [0035] "Pharmaceutically active derivative" refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the activity disclosed herein.

45 [0036] The "tautomers" of the compounds according to formula I are only those wherein R² and/or R⁰ are hydrogen and which display the formula II.

[0037] Quite surprisingly, it was now found that benzazole derivatives according to formula I are suitable pharmaceutically active agents, by effectively modulating, in particular by inhibiting the action of JNK's, notably of JNK 2 and/or 3.

50 [0038] The compounds according to the present invention are those of formula I.



[0039] In the compounds according to formula I

[0040] X is O, S or NR⁰, with R⁰ being H or an unsubstituted or substituted C₁-C₆ alkyl. Most preferred is X = S.

15 [0041] G is selected from the group comprising or consisting of unsubstituted or substituted aryl or heteroaryl substituents, unsubstituted or substituted 3-8-membered saturated or unsaturated ring systems containing at least one heteroatom selected from N, O or S; said 3-8-membered ring system may be fused with a substituted or unsubstituted aryl or heteroaryl system thus providing a bicyclic system.

20 [0042] R¹ is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C₁-C₆-alkoxy, unsubstituted or substituted C₁-C₆-thioalkoxy, unsubstituted or substituted C₁-C₆-alkyl, unsubstituted or substituted C₂-C₆-alkenyl, unsubstituted or substituted C₂-C₆-alkynyl, primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, unsubstituted or substituted C₁-C₆ alkoxy carbonyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxyl, sulfonamide, unsubstituted or substituted hydrazides.

25 [0043] Most preferred substituents R¹ are hydrogen, halogen, C₁-C₆-alkyl and C₁-C₆ alkoxy groups.

[0044] R² is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C₁-C₆-alkyl, unsubstituted or substituted C₂-C₆-alkenyl, unsubstituted or substituted C₂-C₆-alkynyl, unsubstituted or substituted C₁-C₆-alkyl-aryl, unsubstituted or substituted aryl or heteroaryl, unsubstituted or substituted C₁-C₆-alkyl-heteroaryl, -C(O)-OR³, -C(O)-R³, -C(O)-NR³R³', -(SO₂)R³, whereby

30 R³ and R³' are independently selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted C₁-C₆-alkyl aryl, unsubstituted or substituted C₁-C₆-alkyl heteroaryl, R³ and R³' being independently selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted C₁-C₆-alkyl aryl, unsubstituted or substituted C₁-C₆-alkyl heteroaryl.

35 [0045] The present invention also includes the tautomers, its geometrical isomers, the optical active forms, enantiomers, diastereomers of compounds according to formula I, as well as their racemates and also pharmaceutically acceptable salts, as well as the pharmaceutically active derivatives of benzazole of formula I.

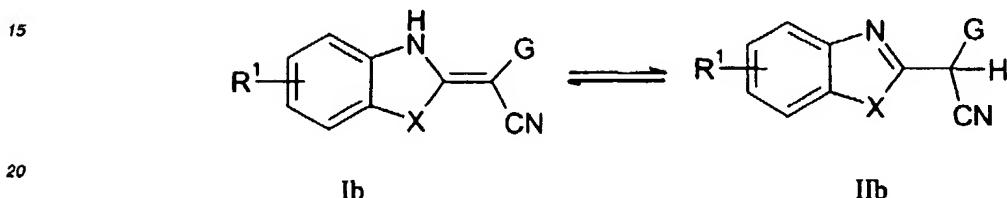
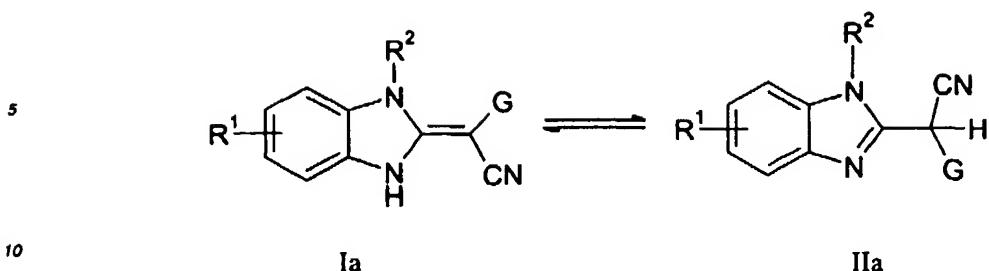
40 [0046] Preferred substituents R² are hydrogen, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted C₁-C₆ alkyl aryl or C₁-C₆ alkyl/heteroaryl group, -C(O)-R³, -C(O)-NR³R³', -(SO₂)R³, whereby R³ and R³' are as above defined. More preferred substituents R² are hydrogen and C₁-C₆-alkyl groups, whereby R² = H is the most preferred embodiment.

45 [0047] Preferred R³ and R³' are hydrogen, C₁-C₆ alkyl, aryl, heteroaryl, C₁-C₆-alkyl aryl, C₁-C₆-alkyl heteroaryl. Most preferred R³ and R³' is hydrogen or C₁-C₆ alkyl.

[0048] Such tautomers mentioned herein are only those wherein R² and/or R⁰ are hydrogen. Said tautomers undergo transformation in solution and an equilibrium between the benzazoles of formula Ia and Ib is established with those of formula IIa and IIb.

50

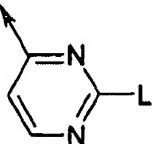
55



[0049] Said tautomers are deemed to be comprised by the present application.

25 **[0050]** Basically, all of the above mentioned aryl or heteroaryl substituents could optionally be further substituted by at least one of the groups selected from substituted or unsubstituted C₁-C₆-alkyl, like trihalomethyl, substituted or unsubstituted C₁-C₆-alkoxy, acetoxy, substituted or unsubstituted C₂-C₆-alkenyl, substituted or unsubstituted C₂-C₆-alkynyl, amino, aminoacyl, aminocarbonyl, C₁-C₆-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfonyl, sulfoxyl, C₁-C₆-thioalkoxy. Preferably said aryl or heteroaryl groups are substituted by halogen, hydroxy, nitro, sulfonyl, e.g. a trifluoromethylsulfonyl group.

30 **[0051]** Particularly preferred benzazole derivatives are those wherein G is an unsubstituted or substituted pyrimidinyl group

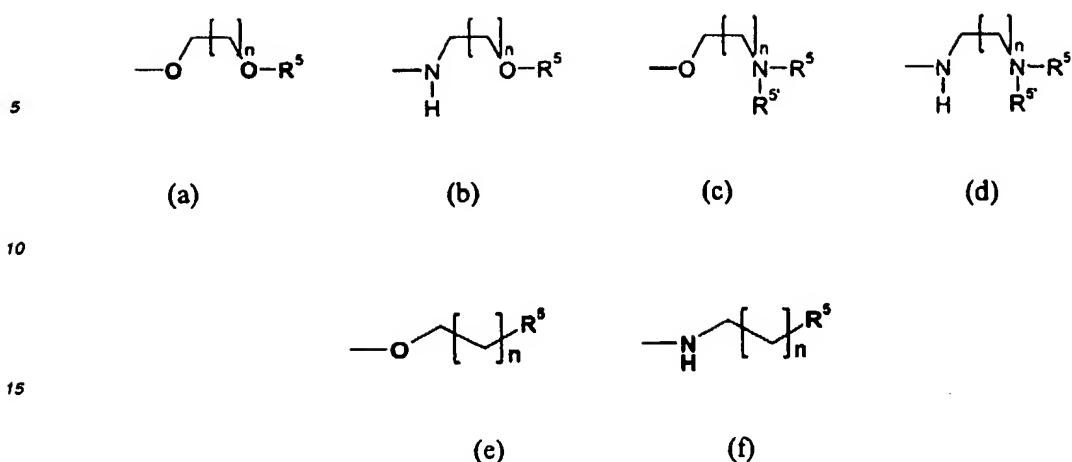


40 wherein L is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted C₁-C₆ alkoxy, unsubstituted or substituted C₁-C₆ thioalkoxy, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, amino-(C₁-C₁₀)alkyl, amino- unsubstituted or substituted (C₁-C₁₀)-alkyl-aryl, amino-unsubstituted or substituted (C₁-C₁₀)alkyl-heteroaryl, unsubstituted or substituted C₁-C₆ alkoxy carbonyl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, sulfonyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted 3-8 membered cycloalkyl, optionally containing at least one heteroatom selected from N, O, S, and unsubstituted or substituted hydrazido groups.

[0052] Particularly preferred benzazole derivatives are those wherein L is a substituted or unsubstituted (C_1 - C_{10})-alkyl group.

[0053] Further particularly preferred benzazole derivatives are those wherein L is a group -N(R^a, R^b) or -OR^a, with R^a and R^b being each independently selected from the group consisting of H, unsubstituted or substituted (C₁-C₁₀)-alkyl, unsubstituted or substituted C₁-C₆ alkyl-aryl, unsubstituted or substituted C₁-C₆-alkyl-heteroaryl, unsubstituted or substituted aryl or heteroaryl and unsubstituted or substituted 4-8 membered saturated or unsaturated cycloalkyl.

55 [0054] Pursuant to a particularly preferred embodiment according to formula I L is selected from



20 wherein n is 1 to 10, preferably 1 to 6

[0055] R^5 and R^5' are independently selected from each other from the group consisting of H, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted or unsubstituted aryl or heteroaryl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl-aryl and substituted or unsubstituted $\text{C}_1\text{-C}_6$ -alkylheteroaryl. Most preferred R^5 is an unsubstituted or substituted imidazolyl.

[0056] Particularly preferred benzazole derivatives are those wherein X is S, R^1 and R^2 are H. Specific examples of 25 compounds of formula I include the following:

30 1,3-benzothiazol-2-yl(2-chloro-4-pyrimidinyl)-acetonitrile
 1,3-benzothiazol-2-yl(2,6-dimethoxy-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl[3-chloro-5-(trifluoromethyl)-2-pyridinyl]acetonitrile
 1,3-benzothiazol-2-yl(2-chloro-6-methyl-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl[2-(methylsulfonyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl(6-chloro-5-nitro-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-oxo-2,3-dihydro-4-pyridinyl)acetonitrile
 35 1,3-benzothiazol-2-yl(2-phenyl-4-quinazolinyl)acetonitrile (6-chloro-1,3-benzothiazol-2-yl)(phenyl)acetonitrile
 1,3-benzothiazol-2-yl(5-chloro-2-pyridinyl)acetonitrile
 1,3-benzothiazol-2-yl(phenyl)acetonitrile
 1,3-benzothiazol-2-yl(6-chloro-2-pyridinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-pyrazinyl)acetonitrile
 40 1,3-benzothiazol-2-yl(2-[(2-(1H-imidazol-4-yl)ethyl]amino)-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl[2-(1-piperazinyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(4-benzyl-1-piperidinyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(4-methyl-1-piperazinyl)-4-pyrimidinyl]acetonitrile
 45 1,3-benzothiazol-2-yl[2-(4-morpholinyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(methylamino)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl(2-(4-[2-(4-morpholinyl)ethyl]-1-piperazinyl)-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-[4-(benzyloxy)-1-piperidinyl]-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-(4-hydroxy-1-piperidinyl)-4-pyrimidinyl)acetonitrile
 50 1,3-benzothiazol-2-yl(2-hydrazino-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-[(2-(dimethylamino)ethyl]amino)-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-(dimethylamino)-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-[(2-methoxyethyl)amino)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl(2-[(2-hydroxyethyl)amino)-4-pyrimidinyl]acetonitrile
 55 1,3-benzothiazol-2-yl(2-(propylamino)-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-[(3-(1H-imidazol-1-yl)propyl]amino)-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-(1-pyrrrolidinyl)-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-[(2-phenylethyl)amino)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl(2-[(2-(2-pyridinyl)ethyl]amino)-4-pyrimidinyl)acetonitrile

1,3-benzothiazol-2-yl[2-[(2-pyridinylmethyl)amino]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[4-(1H-1,2,3-benzotriazol-1-yl)-1-piperidinyl]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[4-(2-pyrazinyl)-1-piperazinyl]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[4-(2-pyrimidinyl)-1-piperazinyl]-4-pyrimidinyl]acetonitrile
 5 1,3-benzothiazol-2-yl[2-[(2-(3-pyridinyl)ethyl)amino]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl(5-bromo-2-[(2-(dimethylamino)ethyl)amino]-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-methoxy-4-pyrimidinyl)-acetonitrile
 (2-chloro-4-pyrimidinyl)(3-methyl-1,3-benzothiazol-2(3H)-ylidene)ethanenitrile

10 [0057] Thereby, the most preferred compounds are those which are selected from the group consisting of:

1,3-benzothiazol-2-yl[2-(methylsulfanyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl(2-chloro-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl[2-(methylamino)-4-pyrimidinyl]acetonitrile
 15 1,3-benzothiazol-2-yl[2-[(2-(1H-imidazol-4-yl)ethyl)amino]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl{2-[(2-hydroxyethyl)amino]-4-pyrimidinyl}acetonitrile
 1,3-benzothiazol-2-yl(2-methoxy-4-pyrimidinyl)acetonitrile

20 [0058] A further aspect of the present invention is related to the use of the benzazole derivatives according to formula I for the preparation of pharmaceutical compositions for the modulation — notably of the inhibition - of the JNK pathway associated disorders, in particular against neuronal disorders and/or against disorders of the immune system as well as said pharmaceutical compositions themselves. Preferred JNK pathways are the JNK2 and/or JNK3.

25 [0059] As pointed out above, the compounds of formula I are suitable to be used as a medicament. Some few of the tautomer compounds falling under the above set out formula II have been disclosed prior to the filing of the present application. However, for most of them no medical or biological activity whatsoever has been described so far. Hence, it is herein reported the novel compounds falling under the above set out generic formula I and the few known tautomer compounds of formula II are indeed suitable for use in treating a whole variety of diseases. Said diseases include disorders of the autoimmune system and neuronal system of mammals, notably of human beings. More specifically, the compounds according to formula I, alone or in the form of a pharmaceutical composition, are useful for the modulation of the JNK pathway, more specifically for the treatment or prevention of disorders associated with abnormal expression or activity of JNK, notably of JNK2 and/or 3. Such an abnormal expression or activity of JNK could be triggered by numerous stimuli (e.g. stress, septic shock, oxidative stress, cytokines) and could lead to out-of-control apoptosis or autoimmune diseases that is frequently involved in the below enumerated disorders and diseases. Hence, the compounds according to formula I could be used for the treatment of disorders by modulating the JNK pathways.

30 35 Said modulation of the JNK pathway could involve its activation, but preferably it involves the inhibition of the JNK pathways, notably of the JNK2 and/or 3. The compounds according to formula I could be employed alone or in combination with further pharmaceutical agents.

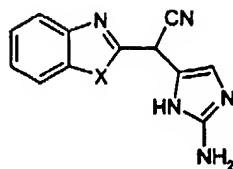
40 [0060] Specifically, the compounds pursuant to formula I are useful for the treatment or prevention of Immuno- and/or neuronal-related diseases or pathological states in which inhibition of JNK2 and/or JNK3 plays a critical role such as epilepsy; neurodegenerative diseases including Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases; spinal cord injury; head trauma, autoimmune diseases including multiple sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis; asthma; septic shock; transplant rejection; cancers including breast, colorectal, pancreatic and cardiovascular diseases including stroke, cerebral ischemia, arteriosclerosis, myocardial infarction, myocardial reperfusion injury.

45 [0061] Quite surprisingly it turned out that the compounds according to formula I do show a considerable activity as inhibitors of JNK2 and/or 3. According to a preferred embodiment, the compounds according to the invention are essentially inactive in view of 2 further MAP Kinases, i.e. p38 and/or ERK2, belonging incidentally to the same family as JNK2 and 3. Hence, the compounds according to the present invention offer the possibility to selectively modulate the JNK pathway, and in particular to come to grips with disorders related to the JNK pathways, while being essentially inactive with regard to other targets like said p38 and ERK2, so that they could indeed be viewed as selective inhibitors. This is of considerable significance, as these related enzymes are generally involved in different disorders, so that for the treatment of a distinct disorder, it is desired to employ a correspondingly selective medicament.

50 [0062] Still a further aspect of the present invention is related to the actually novel benzazole derivatives. Thereby, only some tautomer compounds according to formula II have been disclosed prior to the filing of the present application, whereby nothing is known for the benzazole compounds according to formula I.

55 [0063] The known tautomer compounds of formula II are mentioned in the following documents:

5

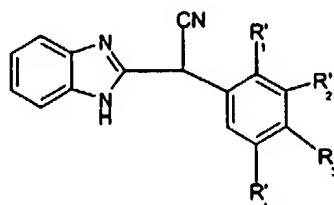


wherein X is NH or S.

10

Heterocycles, 1992, 34, p.1239-1249 discloses benzimidazoles

15



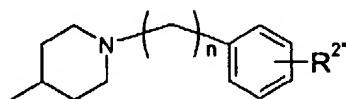
20

wherein X is NH, R1' is H, methyl or -OCH₃, R2' and R3' is H or methyl and R4' is H, methyl or -OCH₃.

25

JP-1'1080'155 is related to compounds of formula IIb, wherein X is S or O, R1' and R2' are both H, G is

30



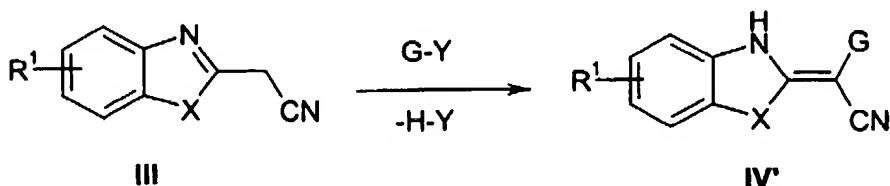
with R2' being H, lower alkyl, lower alkoxy or halogen and with n = 1-4.

35 [0064] DE 198'05'544 discloses dye compounds of formula I, wherein X is O, S or NR, with R being H, C₁-C₄ alkyl or aryl, and wherein G is a 4-diazo-, or 4-diazoniumphenyl group.

[0065] Hence, the entirely novel benzazole derivatives are those of the general formula I and its tautomers according to formula II whereby the above identified known compounds are excluded.

40 [0066] Still a further object of the present invention is a process for preparing the novel benzothiazole derivatives according to formula I. A general synthetic access to the compounds according to formula I is the following:

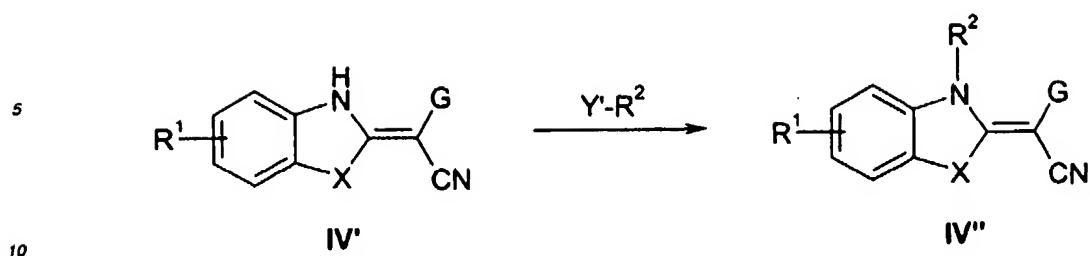
45



50

[0067] The intermediate compound IV* could be transformed in the following way:

55



15

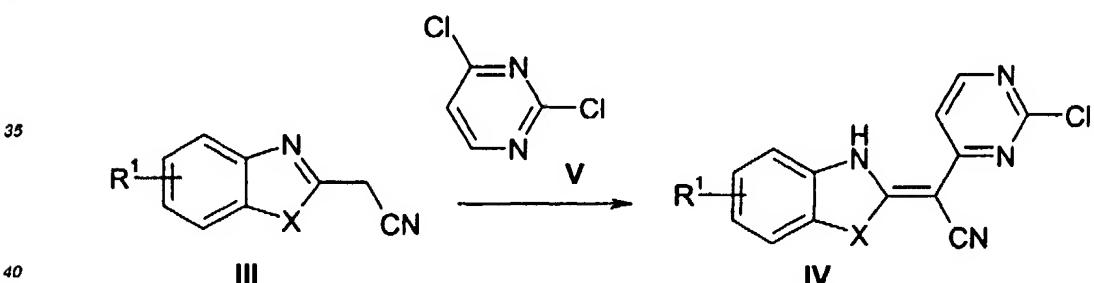
[0068] The starting material III is thereby reacted with an electrophilic compound G-Y, whereby Y is a suitable leaving group. The choice of Y, Y', the reaction method, the reaction conditions, solvents, catalysts will depend on the nature of G and are appropriately selected according to the knowledge of a person skilled in the art. Said method also comprises any modification of G following condensation of G-Y with compound III.

[0069] Preferred compounds of formula I are those wherein G is a heteroaryl group, notably a pyrimidinyl group.

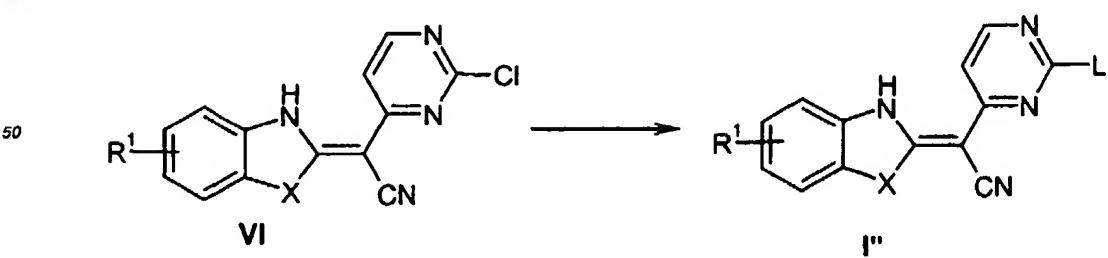


wherein L is as described above. Such compounds are preferably obtained according to the schemes I-III:

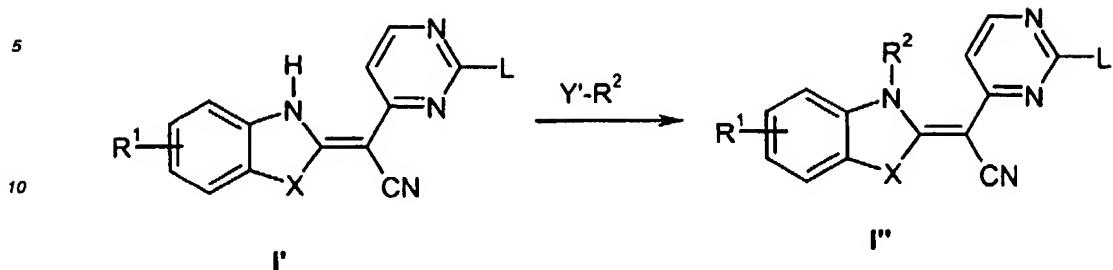
30 **Scheme I**



45 **Scheme II**



Scheme III



[0070] The benzothiazole derivatives exemplified in this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred experimental conditions (i.e., reaction temperatures, time, moles of reagents, solvents, etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by one skilled in the art by routine optimisation procedures.

[0071] In the above schemes I to III, R¹R² and X are as described above.

[0072] In Scheme I, the compounds of formula III may be converted to the compounds of formula IV by treatment of the starting compounds with a base such as sodium hydride, potassium hydride and the like in an anhydrous inert atmosphere in polar solvents like DMF or THF at a temperature in the range of about -78°C to 25°C (Chabaka L.M. et al, *Pol. J. Chem.*, 1994, 1317-1326) for about an hour followed by the drop wise addition of unsubstituted or substituted halogenated heteroaryl derivatives of formula V as described above, being most preferably pyridine, pyrimidine derivatives, in solvents such as DMF or THF and then gradually warming the mixture to a temperature in the range of about 25°C to 70°C for about 1 to 18 hours to afford compounds of formula IV wherein R¹, and X are as described above and R² is hydrogen.

[0073] Benzazole of formula III are either commercially available, such as from Maybridge Chemical Co. Ltd or can be prepared from commercially available compounds by conventional procedures (Loew et al. US4,064,136, Lorenz M, DE1963542), wherein R¹ and X are as defined above and are most preferably respectively H and S.

[0074] Unsubstituted or substituted halogenated heteroaryl of formula V are also either commercially available, such as from Aldrich, Fluka, Sigma and the like or can be prepared from known compounds by conventional procedures (WO 98/24782). Preferred halogenated heteroaryl as starting materials include 2,4-dichloropyrimidine, 2-chloropyridine and the like.

[0075] In Scheme II the compounds of formula VI, wherein R¹, R² and X are as defined above may be converted to the compounds of formula I" by the treatment with groups of type L, wherein L is as described above. Most preferably, L is an amine, an alcohol or a thioalcohol defined as described above.

[0076] The reaction is performed in solution in solvents such as DMF, NMP, DMSO or alcohols for example EtOH, MeOH or iPrOH, most preferably in EtOH, in the presence of an organic base such as Et₃N, DIPEA or the like, most preferably Et₃N, at a temperature in the range of about 25 to 80°C. In a preferred method, the starting compounds are heated at 70°C in solution in EtOH in the presence of Et₃N.

[0077] Amines are either commercially available or can be prepared from known compounds by conventional procedures known by one skilled in the art. Preferred amines as starting materials include methylamine, N,N-dimethylaminoethylamine, morpholine histamine and the like.

[0078] Alcohols or thioalcohols are either commercially available or can be prepared from known compounds by conventional procedures known by one skilled in the art. Preferred alcohols or thioalcohols as starting materials include MeOH, MeSH and the like.

[0079] In Scheme III the compounds of formula I' wherein R² is hydrogen and R¹ and X are as above described, most preferably H and S, may be converted to the compounds of formula I" wherein R² is different from hydrogen by the treatment of the starting compound with electrophiles Y'-R² such as such as alkyl or benzyl halides and acyl chlorides at a temperature in the range of 25°C to 80°C in the presence of a base such as potassium carbonate, sodium hydroxide, sodium hydride and the like in a solvent such as DMSO, DMF, acetone and the like in an anhydrous inert atmosphere. In a preferred method, the starting compounds are shaken at 25°C in solution in DMSO in the presence of potassium carbonate.

[0080] Electrophiles are either commercially available or can be prepared from known compounds by conventional procedures known by one skilled in the art. Preferred electrophiles as starting materials include methyl iodide and

acetyl chloride.

[0081] If the above set out general synthetic methods are not applicable for the obtention of compounds of formula I, suitable methods of preparation known by a person skilled in the art should be used.

[0082] A final aspect of the present invention is related to the use of the compounds according to formula I for the modulation of the JNK pathway, the use of said compounds for the preparation of pharmaceutical compositions for the modulation of the JNK pathway as well as the formulations containing the active compounds according to formula I. Said modulation of the JNK pathway is viewed as a suitable approach of treatment for various disorders. When employed as pharmaceuticals, the benzazole derivatives of the present invention are typically administered in the form of a pharmaceutical composition. Hence, pharmaceutical compositions comprising a compound of formula I and a pharmaceutically acceptable carrier, diluent or excipient therefore are also within the scope of the present invention. A person skilled in the art is aware of a whole variety of such carrier, diluent or excipient compounds suitable to formulate a pharmaceutical composition. Also, the present invention provides compounds for use as a medicament. In particular, the invention provides the compounds of formula I for use as JNK inhibitor, notably for JNK2 and JNK3, for the treatment of disorders of the immune as well as the neuronal system of mammals, notably of humans, either alone or in combination with other medicaments.

[0083] The compounds of the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous use). Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

[0084] When employed as pharmaceuticals, the benzazole derivatives of this invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0085] The pharmaceutical compositions of these inventions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, the compounds are preferably formulated as either injectable or oral compositions. The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the benzazole compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[0086] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatine; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0087] Injectable compositions are typically based upon injectable sterile saline or phosphate buffered saline or other injectable carriers known in the art. As above mentioned, the benzazole derivatives of formula I in such compositions is typically a minor component, frequently ranging between 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

[0088] The above described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in Part 8 of *Remington's Pharmaceutical Sciences*, 17th Edition, 1985, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

[0089] The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can also be found in the

incorporated materials in *Remington's Pharmaceutical Sciences*.

[0090] In the following the present invention shall be illustrated by means of some examples which are not construed to be viewed as limiting the scope of the Invention.

[0091] In the following the present invention shall be illustrated by means of some examples which are not construed

5 to be viewed as limiting the scope of the Invention. The HPLC, NMR and MS data provided in the examples described below were obtained as followed : HPLC: column Waters Symmetry C8 50 x 4.6 mm, Conditions: a- MeCN/H₂O 0.09% TFA, 0 to 100% (10 min); b- MeCN/H₂O 0.09% TFA, 0 to 100% (20 min); Mass spectrum : Perkin Elmer API 150 EX (APCI); ¹H-NMR : Brucker DPX-300MHz.

10 **Examples**

Example 1 : Preparation of 1,3-benzothiazol-2-yl(2-chloro-4-pyrimidinyl)-acetonitrile 1

[0092] To a stirred suspension of NaH (60% in oil, 0.92 g, 23 mmol) in dry DMF (12 ml) was added drop wise under inert atmosphere a solution of 1,3-benzothiazol-2-yl-acetonitrile (2 g, 11.5 mmol) in dry DMF (12 ml). After 1h30 stirring at r.t., a solution of 2,4-dichloropyrimidine (1.71 g, 11.5 mmol) in dry DMF (12 ml) was added dropwise. The reaction mixture was allowed to stir under inert atmosphere at r.t. until complete disappearance of the starting material. The reaction was quenched by addition of water then the product was extracted with AcOEt (6X). The combined extracts were washed with brine, dried over MgSO₄ and the solvent evaporated. The crude yellow residue was dried under vacuum at 40°C, affording 2 g (61%) of the title compound as a yellow powder : mp 246°C dec.; MS : 286.8 (M+1); HPLC (Conditions a, 268 nm) 97%, rt. 5.66 min ; ¹HNMR (DMSO-d6) δ 13.25 (br s, 1H, exchangeable), 8.09 (d, J = 4.14 Hz, 1H), 7.90 (d, J = 7.53 Hz, 1H), 7.61 (d, J = 7.92 Hz, 1H), 7.39-7.34 (m, 1H), 7.20-7.15 (m, 1H), 6.96 (br d, 1H) CHN analysis : C₁₃H₇CIN₄S : Calculated :C, 54.19 %, H 2.48 %, N 19.45 %; Found : C 53.35 %, H 2.77 %, N 17.62 %

[0093] Upon using the procedure described above in the example 1 and the appropriate starting material and reagents, the following additional benzothiazole derivatives of formula I could be obtained.

1,3-benzothiazol-2-yl(2,6-dimethoxy-4-pyrimidinyl)acetonitrile 2

(Y = 11.3 %); MS : 313.0 (M+1); HPLC (Conditions a, 372 nm) 97%, rt. 13.90 min

¹HNMR (DMSO-d6) δ 12.78 (br s, 1H, exchangeable), 7.85 (d, J = 7.73 Hz, 1H), 7.55 (d, J = 7.97 Hz, 1H), 7.42-7.37 (m, 1H), 7.25-7.20 (m, 1H), 6.19 (s, 1H), 4.07 (s, 3H), 3.86 (s, 3H)

1,3-benzothiazol-2-yl[3-chloro-5-(trifluoromethyl)-2-pyridinyl]acetonitrile 3

(Y = 81.1 %); MS : 353.8 (M+1); HPLC (Conditions b, 269 nm) 91%, rt. 16.36 min.

¹HNMR (DMSO-d6) δ 12.81 (br s, 1H, exchangeable), 8.81 (d, J < 1 Hz, 1H), 8.22 (s, 1H), 7.86 (d, J = 7.63 Hz, 1H), 7.69 (d, J = 7.99 Hz, 1H), 7.47-7.42 (m, 1H), 7.30-7.25 (m, 1H)

1,3-benzothiazol-2-yl(2-chloro-6-methyl-4-pyrimidinyl)acetonitrile 4

(Y = 42.8 %); MS : 300.8 (M+1); HPLC (Conditions b, 254 nm) 92%; rt. 13.91 min. ¹HNMR (DMSO-d6) δ 13.22 (br s, 1H, exchangeable), 7.96 (d, J = 7.79 Hz, 1H), 7.63 (d, J = 8.17 Hz, 1H), 7.48-7.42 (m, 1H), 7.30-7.25 (m, 1H), 7.07 (s, 1H), 2.39 (s, 3H)

1,3-benzothiazol-2-yl[2-(methylsulfonyl)-4-pyrimidinyl]acetonitrile 5

(Y = 73.5 %); MS : 298.8 (M+1); HPLC (Conditions a, 254 nm) 99%, rt. 4.64 min

¹HNMR (DMSO-d6) δ 13.01 (br s, 1H), 8.10 (br d, 1H), 7.93 (d, J = 7.75 Hz, 1H), 7.66 (d, J = 8.01 Hz, 1H), 7.45-7.40 (m, 1H), 7.29-7.23 (m, 1H), 6.84 (br d, 1H), 2.71 (s, 3H)

1,3-benzothiazol-2-yl(6-chloro-5-nitro-4-pyrimidinyl)acetonitrile 6

(Y = 7.3 %); MS : 332.0 (M+1); HPLC (Conditions a, 270 nm) 86%, rt. 6.10 min

¹HNMR (DMSO-d6) δ 8.80 (s, 1H), 8.00 (d, J = 7.91 Hz, 1H), 7.77 (d, J = 8.29 Hz, 1H), 7.53-7.47 (m, 1H), 7.38-7.32 (m, 1H)

1,3-benzothiazol-2-yl(2-pyrimidinyl)acetonitrile 7

(Y = 9.7 %); MS : 253.0 (M+1); HPLC (Conditions a, 236 nm) 92%, rt. 5.06 min

¹HNMR (DMSO-d6) δ 12.63 (br s, 1H, exchangeable), 8.71 (d, J = 4.84 Hz, 2H), 7.84 (d, J = 7.98 Hz, 1H), 7.56 (d, J = 7.91 Hz, 1H), 7.43-7.37 (m, 1H), 7.24-7.19 (m, 1H), 7.05 (t, J = 4.84 Hz, 1H)

1,3-benzothiazol-2-yl(2-oxo-2,3-dihydro-4-pyridinyl)acetonitrile 8

(Y = 36.2 %); MS : 269.0 (M+1); HPLC (Conditions a, 271 nm) 90%, rt. 525 min

¹HNMR (DMSO-d6) δ 12.86 (br s, 1H, exchangeable), 11.82 (br s, 1H, exchangeable), 8.06 (d, J = 8 Hz, 1H), 7.89 (d, J = 8.04 Hz, 1H), 7.58 (d, J = 7.28 Hz, 1H), 7.53-7.48 (m, 1H), 7.40-7.35 (m, 1H), 6.11 (d, J = 7.31 Hz, 1H)

5 1,3-benzothiazol-2-yl(2-phenyl-4-quinazolinyl)acetonitrile **9**

(Y = 83.6 %); MS : 379.0 (M+1); HPLC (Conditions a, 248 nm) 86%, rt. 7.09 min

¹H NMR (DMSO-d6) \square 12.86 (br s, 1H, exchangeable), 9.03 (d, J = 8.29 Hz, 1H), 8.43-8.34 (m, 2H), 7.99 (d, J = 7.91 Hz, 1H), 7.87 (d, J = 7.91 Hz, 1H), 7.83-7.67 (m, 5H), 7.60-7.53 (m, 1H), 7.47-7.42 (m, 1H), 7.33-7.28 (m, 1H).

10 (6-chloro-1,3-benzothiazol-2-yl)(phenyl)acetonitrile **10**

(Y = 4.1%); MS : 285.0 (M+1); HPLC (Conditions a, 265 nm) 94%; rt. 6.77 min

¹H NMR (CDCl₃) \square 7.97 (d, J = 8.71 Hz, 1H), 7.79 (d, J = 2.14 Hz, 1H), 7.54-7.50 (m, 2H), 7.48-7.40 (m, 4H [3+1]), 5.59 (s, 1H)

15 1,3-benzothiazol-2-yl(5-chloro-2-pyridinyl)acetonitrile **11**

(Y = 4.7%) MS : 286 (M+1); HPLC (Conditions a, 254 nm) 95%; rt. 7.05 min

¹HNMR (DMSO-d6) δ 12.56 (br s, 1H, exchangeable), 8.55 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 8.66, 2.57 Hz, 1H), 7.81 (d, J = 7.91 Hz, 1H), 7.51 (d, J = 7.91 Hz, 1H), 7.41-7.36 (m, 1H), 7.37-7.34 (m, 1H), 7.22-7.17 (m, 1H)

20 1,3-benzothiazol-2-yl(phenyl)acetonitrile **12**

(Y = 7.6%); MS : 251.0 (M+1); HPLC (Conditions a, 254 nm) 99%, rt. 6.25 min

¹HNMR (CDCl₃) δ 8.06 (d, J = 7.89 Hz, 1H), 7.82 (d, J = 7.77 Hz, 1H), 7.56-7.37 (m, 7H), 5.62 (s, 1H)

25 1,3-benzothiazol-2-yl(6-chloro-2-pyridinyl)acetonitrile **13**

(Y = 36.2%); MS 286.0 (M+1); HPLC (Conditions a, 364 nm) : 99%, rt. 7.02 min

¹HNMR (DMSO-d6) δ 12.44 (s, 1H), 7.64 (d, J = 7.54 Hz, 1H), 7.57 (t, J = 7.91 Hz, 1H), 7.30 (d, J = 7.91 Hz, 1H), 7.20-7.14 (m, 1H), 7.06 (d, J = 8.29 Hz, 1H), 7.00-6.96 (m, 1H), 6.86 (d, J = 7.54 Hz, 1H)

30 1,3-benzothiazol-2-yl(2-pyrazinyl)acetonitrile **14**

(Y = 46.9%); MS : 253.0 (M+1); HPLC (Conditions a, 327 nm) 95%, rt. 5.21 min

¹HNMR (DMSO-d6) δ 12.80 (s, 1H), 8.63 (d, J = 1.51 Hz, 1H), 8.56-8.53 (m, 1H), 8.21 (d, J = 2.64 Hz, 1H), 7.85 (d, J = 7.91 Hz, 1H), 7.54 (d, J = 7.91 Hz, 1H), 7.44-7.38 (m, 1H), 7.25-7.20 (m, 1H)

Example 2 : Preparation of 1,3-benzothiazol-2-yl(2-[2-(1H-imidazol-4-yl)ethyl]amino)-4-pyrimidinyl)acetonitrile **15**

35 [0094] To a suspension of **1** (0.1g, 0.35 mmol) in dry EtOH (3 ml) was added Et₃N (0.05 ml, 0.35 mmol) and histamine (0.078g, 0.70 mmol). After sonication, the yellow solution was shaken at 70°C for 3 days. The yellow precipitate formed was filtered off and washed with H₂O (2X) then EtOH (3X) and dried under vacuum at 40°C, affording 47 mg (37%) of the title compound as a bright yellow powder: mp 257-258°C,

40 **13** was taken up in a mixture of DCM/TFA . The yellow fluffy solid formed by addition of ether was filtered off, washed with ether (3X) then dried under vacuum at 40°C, affording 36 mg (29%) of the title compound as a yellow powder: mp 247-249°C, 362.0 (M+1); HPLC (Conditions a, 265 nm): 98%, rt. 2.87 min; ¹H NMR (DMSO-d6) : δ 14.25 (br s, 2H, exchangeable), 11.05 (br s, 1H, exchangeable), 9.03 (s, 1H), 7.94-7.87 (m, 1H), 7.74-7.71 (m, 2H), 7.57-7.52 (m, 2H), 7.42-7.37 (m, 1H), 7.24-7.19 (m, 1H), 6.40 (d, J = 7.1Hz, 1H), 3.97-3.55 (m, 3 H [2+1]), 3.11-3.05 (m, 2H).

45 CHN analysis : C18H15N7S. 2TFA: Calculated :C 44.83 %, H 2.91%, N 16.63%; Found : C 44.59 %, H 3.18%, N 16.43%

[0095] Upon using the procedure described above in the example 2 and the appropriate starting material and reagents, the following additional benzothiazole derivatives of formula II could be obtained.

50 1,3-benzothiazol-2-yl[2-(1-piperazinyl)-4-pyrimidinyl]acetonitrile (2 TFA) **16**

(Y = 37%); MS : 337.2 (M+1); HPLC (Conditions a, 271 nm) 96%, rt. 2.58 min

¹H NMR (DMSO-d6) : δ 9.13 (br s, 2H, exchangeable), 7.96 (br d, 1H), 7.90 (d, J = 7.74 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1H), 7.45-7.40 (m, 1H), 7.29-7.24 (m, 1H), 6.58 (d, J = 6.0 Hz, 1H), 4.70-3.60 (m, 5H [4+1]), 3.38-3.20 (m, 4H).

55 1,3-benzothiazol-2-yl[2-(4-benzyl-1-piperidinyl)-4-pyrimidinyl]acetonitrile (TFA) **17**

(Y = 52%); MS : 426.0 (M+1); HPLC (Conditions a, 394 nm) 99%, rt. 5.42 min

¹H NMR (DMSO-d6) : δ 7.94 (d, J = 7.78 Hz, 1 H), 7.72-7.69 (m, 2H), 7.46-7.41 (m, 1H), 7.32-7.24 (m, 3H [1+2]), 7.21-7.18 (m, 3H), 6.50 (d, J = 6.2 Hz, 1H), 4.55-4.51 (m, 2H), 4.35-3.45 (m, 1H), 3.16-3.04 (m, 2H), 2.56 (d, J = 7.0 Hz, 2H), 2.00-1.85 (m, 1H), 1.81-1.72 (m, 2H), 1.34-1.21 (m, 2H)

1,3-benzothiazol-2-yl[2-(4-methy)-1-piperazinyl]-4-pyrimidinyl]acetonitrile (2 TFA) **18**

(Y = 30%); MS : 351.0 (M+1); HPLC (Conditions a, 271 nm) 99%, rt. 2.54 min

5 ¹H NMR (DMSO-d6) δ 10.10 (br s, 2H, exchangeable), 8.05 (br d, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.45-7.40 (m, 1H), 7.29-7.24 (m, 1H), 6.60 (d, J = 5.8 Hz, 1H), 4.95-4.70 (m, 2H), 4.42-3.68 (m, 1H), 3.67-3.50 (m, 2H), 3.48-3.31 (m, 2H), 3.26-3.05 (m, 2H), 2.86 (s, 3H).

1,3-benzothiazol-2-yl[2-(4-morpholinyl)-4-pyrimidinyl]acetonitrile (TFA) **19**

(Y = 55%); MS : 338.0 (M+1); HPLC (Conditions a, 270 nm) 99%, rt. 3.51 min

10 ¹H NMR (DMSO-d6) δ 7.94 (d, J = 7.8 Hz, 1H), 7.79 (br d, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.45-7.40 (m, 1H), 7.30-7.25 (m, 1H), 6.54 (d, J = 6.3 Hz, 1H), 4.40-3.65 (m, 9H [1+8])

1,3-benzothiazol-2-yl[2-(methylamino)-4-pyrimidinyl]acetonitrile (TFA salt) **20**

(Y = 11%); MS : 282.0 (M+1); HPLC (Conditions a, 270 nm) 97%, rt. 3.39 min

15 ¹H NMR (DMSO-d6) δ 11.70 (v br s, 1H, exchangeable) 8.15-7.90 (m, 2H [1+1 exchangeable]), 7.85-7.55 (m, 2H), 7.46-7.41 (m, 1H), 7.30-7.25 (m, 1H), 6.43 (d, J = 6.0 Hz, 1H), 4.81-3.78 (m, 1H), 3.10 (s, 3H)

1,3-benzothiazol-2-yl[2-(4-[2-(4-morpholinyl)ethyl]-1-piperazinyl)-4-pyrimidinyl]acetonitrile (3 TFA) **21**

(Y = 78%); MS : 450.2 (M+1); HPLC (Conditions a, 270 nm) 99 %, rt. 2.67min

20 ¹HNMR (DMSO-d6) δ 7.91 (br d, 1H), 7.86 (d, J = 7.73 Hz, 1H), 7.66 (d, J = 8.01 Hz, 1H), 7.45-7.40 (m, 1H), 7.29-7.24 (m, 1H), 6.56 (d, J = 5.94 Hz, 1H), 4.10-3.93 (m, 4H), 3.85-3.42 (m, 5H), 3.32-3.23 (m, 4H), 3.18-3.04 (m, 8H)

1,3-benzothiazol-2-yl {2-[4-(benzyloxy)-1-piperidinyl]-4-pyrimidinyl} acetonitrile (TFA) **22** (Y = 76.2%); MS : 442.2 (M+1); HPLC (Conditions a, 268 nm) 99%, rt. 5.00 min

25 ¹HNMR (DMSO-d6) δ 7.92 (d, J = 7.94 Hz, 1H), 7.70 (d, J = 8.08 Hz, 1H), 7.65 (br d, 1H), 7.43-7.35 (m, 5H), 7.32-7.22 (m, 2H), 6.46 (d, J = 6.6 Hz, 1H), 4.59 (s, 2H), 4.20-4.06 (m, 2H), 3.81-3.72 (m, 1H), 3.70-3.59 (m, 2H), 3.57-3.20 (m, 1H), 2.09-1.96 (m, 2H), 1.77-1.61 (m, 2H)

1,3-benzothiazol-2-yl[2-(4-hydroxy-1-piperidinyl)-4-pyrimidinyl]acetonitrile (TFA) **23**

(Y = 14%); MS : 352 (M+1); HPLC (Conditions a, 271 nm) 97%, rt. 3.21 min

30 ¹HNMR (DMSO-d6) δ 7.95 (d, J = 7.79 Hz, 1H), 7.72-7.65 (m, 2H), 7.45-7.40 (m, 1H), 7.28-7.23 (m, 1H), 6.48 (d, J = 6.07 Hz, 1H), 4.60-3.75 (m, 5H), 3.58-3.51 (m, 2H), 1.95-1.82 (m, 2H), 1.55-1.42 (m, 2H)

1,3-benzothiazol-2-yl[2-hydrazino-4-pyrimidinyl]acetonitrile (TFA) **24**

(Y = 60%) 283.0 (M+1); HPLC (271 nm) : 98%, rt. 3.17 min

35 ¹H NMR (DMSO-d6): □□ 9.78 (br s, 1H, exchangeable), 7.89-7.75 (m, 4H), 7.48-7.43 (m, 1H), 7.32-7.27 (m, 1H), 6.53 (br d, 1H), 4.25-3.40 (m, 1H).

1,3-benzothiazol-2-yl[2-[(2-(dimethylamino)ethyl)amino]-4-pyrimidinyl]acetonitrile (2 TFA) **25**

(Y = 30%); 339.0 (M+1); HPLC (Conditions a, 270 nm): 99%, rt. 2.69 min

40 ¹H NMR (DMSO-d6): δ 11.85 (v br s, 1H, exchangeable), 9.59(br s, 1H), 7.90 (br d, 2H), 7.73 (d, J = 7.9 Hz, 1H), 7.60 (br d, 1H), 7.43-7.38 (m, 1H), 7.27-7.22 (m, 1H), 6.43 (d, J = 6.8 Hz, 1H), 4.25-3.70 (m, 3H [2+1]), 3.51-3.41 (m, 2H), 2.87 (s, 6H).

45 1,3-benzothiazol-2-yl[2-(dimethylamino)-4-pyrimidinyl]acetonitrile **26**

(Y = 12%); 295.8 (M+1); HPLC (Conditions a, 270 nm) : 99%, rt. 3.50 min

¹H NMR (DMSO-d6): δ 11.20,(br s, 1H), 7.88 (d, J = 7.76 Hz 1H), 7.69 (d, J = 8 Hz 1H), 7.46 (br d, 1H), 7.38-7.33 (m, 1H), 7.20-7.16 (m, 1H), 6.38 (d, J = 6.9 Hz, 1H), 3.26 (s, 6H).

50 1,3-benzothiazol-2-yl[2-[(2-methoxyethyl)amino]-4-pyrimidinyl]acetonitrile **27**

(Y = 54%); 326.0 (M+1); HPLC (Conditions a, 273 nm) : 99%, rt. 3.66 min

55 ¹HNMR (DMSO-d6) δ 10.83 (s, 1H), 7.85 (d, J = 7.54 Hz, 1H), 7.72 (d, J = 7.91 Hz, 1H), 7.60 (br s, 1H), 7.44 (d, J = 6.78 Hz, 1H), 7.38-7.33 (m, 1H), 7.22-7.16 (m, 1H), 6.33 (d, J = 7.16 Hz, 1H), 3.82-3.74 (m, 2H), 3.62 (t, J = 5.27 Hz, 2H), 3.31 (s, 3H)

55 1,3-benzothiazol-2-yl[2-[(2-hydroxyethyl)amino]-4-pyrimidinyl]acetonitrile **28**

(Y = 80%); 312.2 (M+1); HPLC (Conditions a, 273 nm) : 99%, rt. 3.16 min

¹HNMR (DMSO-d6) δ 10.85 (s, 1H), 7.86 (d, J = 7.91 Hz, 1H), 7.71 (d, J = 7.91 Hz, 1H), 7.57 (br s, 1H), 7.44 (d,

EP 1 110 957 A1

J = 7.16 Hz, 1H), 7.38-7.32 (m, 1H), 7.21-7.16 (m, 1H), 6.32 (d, *J* = 7.16 Hz, 1H), 4.92 (br s, 1H), 3.68 (br s, 4H)

1,3-benzothiazol-2-yl[2-(propylamino)-4-pyrimidinyl]acetonitrile 29

(Y = 81%); 310.0 (M+1); HPLC (Conditions a, 273 nm) : 95%, rt. 4.04 min

¹HNMR (DMSO-*d*6) δ 10.91 (br s, 1H), 7.84 (d, *J* = 7.54 Hz, 1H), 7.71 (d, *J* = 8.29 Hz, 1H), 7.62 (br s, 1H), 7.42 (d, *J* = 6.78 Hz, 1H), 7.38-7.32 (m, 1H), 7.21-7.16 (m, 1H), 6.31 (d, *J* = 7.53 Hz, 1H), 3.42-3.33 (m, 2H), 1.71-1.64 (m, 2H), 1.02-0.97 (m, 3H)

1,3-benzothiazol-2-yl[2-[(3-(1H-imidazol-1-yl)propyl)amino]-4-pyrimidinyl]acetonitrile (TFA) 30

(Y = 57%), 376.0 (M+1); HPLC (Conditions a, 270 nm) : 98%, rt. 2.80 min

¹H NMR (DMSO-*d*6): δ 14.40 (br s, 1 H, exchangeable), 11.60 (br s, 1 H, exchangeable), 9.18 (s, 1H), 8.13 (br d, 1H), 7.92-7.85 (m, 2H), 7.74-7.59 (m, 3H), 7.43-7.39 (m, 1H), 7.28-7.23 (m, 1H), 6.40 (d, *J* = 7.2 Hz, 1H), 4.35 (t, *J* = 6.8 Hz, 2H), 3.70-3.45 (m, 2H), 5.05-4.20 (m, 1H), 2.35-2.10 (m, 2H)

1,3-benzothiazol-2-yl[2-(1-pyrrolidinyl)-4-pyrimidinyl]acetonitrile 31

(Y = 27 %), mp = 270-272°C, MS :322.0 (M+1); HPLC (Conditions a, 372 nm) : 98%, rt. 3.90 min

¹H NMR (DMSO-*d*6): δ 11.30 (v br s, 1 H, exchangeable), 7.86 (d, *J* = 7.2 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 6.8 Hz, 1H), 7.35-7.30 (m, 1H), 7.17-7.12 (m, 1H), 6.33 (d, *J* = 6.8 Hz, 1H), 3.90-3.45 (m, 4H), 2.08-1.94 (m, 4H).

1,3-benzothiazol-2-yl[2-[(2-phenylethyl)amino]-4-pyrimidinyl]acetonitrile 32

(Y = 46.1%); mp = 256°C dec., [M+H]⁺ = 371.8; HPLC (Conditions a, 270 nm) : 99%, rt. 4.64 min

¹HNMR (DMSO-*d*6) δ 11.04 (br s, 1H), 7.71 (d, *J* = 8.29 Hz, 1H), 7.64-7.61 (m, 2H), 7.45 (d, *J* = 7.16 Hz, 1H), 7.37-7.32 (m, 5H), 7.29-7.26 (m, 1H), 7.20-7.16 (m, 1H), 6.33 (d, *J* = 7.17 Hz, 1H), 3.94-3.81 (m, 2H), 2.99 (t, *J* = 7.54 Hz, 2H)

1,3-benzothiazol-2-yl(2-[(2-(2-pyridinyl)ethyl)amino]-4-pyrimidinyl)acetonitrile (2 TFA) 33

(Y = 80%); mp = 247°C dec., MS : 373.2 (M+1); HPLC (Conditions a, 266 nm): 99%, rt. 2.85 min

¹HNMR (DMSO-*d*6) δ 8.70 (d, *J* = 5.28 Hz, 1H), 8.15-8.10 (m, 1H), 7.88 (br s, 1H), 7.75-7.72 (m, 2H), 7.67 (d, *J* = 7.91 Hz, 1H), 7.61-7.50 (m, 2H), 7.44-7.39 (m, 1H), 7.28-7.23 (m, 1H), 6.44 (d, *J* = 7.14 Hz, 1H), 4.65-3.60 (m, 3H [2+1]), 3.32-3.28 (m, 2H)

CHN analysis : C20H16N6S. 2TFA: Calculated :C 47.29 %, H 3.14%, N 13.79%; Found : C 47.47 %, H 3.21%, N 13.71%

1,3-benzothiazol-2-yl[2-[(2-pyridinylmethyl)amino]-4-pyrimidinyl]acetonitrile (2 TFA) 34

(Y = 52%); mp = 250°C dec., MS :359.0 (M+1); HPLC (Conditions a, 266 nm) : 99%, rt.2.84 min

¹HNMR (DMSO-*d*6) δ 8.66 (d, *J* = 4.9 Hz, 1H), 8.38 (br s, 1H), 7.99-7.94 (m, 1H), 7.82 (d, *J* = 7.91 Hz, 1H), 7.71-7.69 (m, 2H), 7.64 (d, *J* = 7.91 Hz, 1H), 7.45-7.38 (m, 2H), 7.28-7.23 (m, 1H), 6.48 (d, *J* = 6.78 Hz, 1H), 5.00 (br s, 2H), 5.15-4.05 (m, 2H).

CHN analysis : C19H14N6S. 2TFA: Calculated :C 47.10 %, H 2.75%, N 14.33 %; Found : C 46.93 %, H 2.96 %, N 14.24 %

1,3-benzothiazol-2-yl {2-[4-(1H-1,2,3-benzotriazol-1-yl)-1-piperidinyl]-4-pyrimidinyl} acetonitrile (TFA) 35

(Y = 65%); MS : 453.2 (M+1); HPLC (Conditions a, 254 nm): 90%, rt. 4.39 min

¹HNMR (DMSO-*d*6) δ 8.06 (d, *J* = 8.29 Hz, 1H), 8.01 (d, *J* = 8.67 Hz, 1H), 7.91 (d, *J* = 7.91 Hz, 1H), 7.80 (br d, 1H), 7.70 (d, *J* = 8.29 Hz, 1H), 7.60-7.55 (m, 1H), 7.44-7.39 (m, 1H), 7.27-7.22 (m, 1H), 8.01-7.22 (very br m, 1H), 6.56 (d, *J* = 6.42 Hz, 1H), 5.40-5.33 (m, 1H), 4.79-4.74 (m, 2H), 4.90-3.90 (m, 1H), 3.57-3.50 (m, 2H), 2.37-2.27 (m, 4H)

1,3-benzothiazol-2-yl[2-[4-(2-pyrazinyl)-1-piperazinyl]-4-pyrimidinyl]acetonitrile (TFA) 36

(Y = 88%); MS : 415.2 (M+1); HPLC (Conditions a, 254 nm): 99%, rt. 3.74 min

¹HNMR (DMSO-*d*6) δ 8.39 (br d, 1H), 8.13 (dd, *J* = 2.64, 1.51 Hz, 1H), 7.97 (d, *J* = 7.91 Hz, 1H), 7.88 (d, *J* = 2.63 Hz, 1H), 7.79 (br d, 1H), 7.71 (d, *J* = 7.91 Hz, 1H), 7.46-7.41 (m, 1H), 7.31-7.26 (m, 1H), 8.13-7.26 (very br m, 1H), 6.53 (d, *J* = 6.78 Hz, 1H), 4.06-3.96 (m, 4H), 3.87-3.77 (m, 4H), 4.60-3.65 (m, 1H)

1,3-benzothiazol-2-yl[2-[4-(2-pyrimidinyl)-1-piperazinyl]-4-pyrimidinyl]acetonitrile (TFA) 37

(Y = 85%); MS :415.2 (M+1); HPLC (Conditions a, 254 nm) : 99%, rt. 3.81min

¹HNMR (DMSO-*d*6) δ 8.44 (d, *J* = 4.52 Hz, 2H), 8.03 (d, *J* = 7.91 Hz, 1H), 7.83 (br d, 1H), 7.78 (d, *J* = 7.91 Hz, 1H), 7.48-7.43 (m, 1H), 7.32-7.27 (m, 1H), 8.44-7.27 (very br m, 1H), 6.71-6.68 (m, 1H), 6.56 (d, *J* = 6.4 Hz, 1H),

5.15-4.10 (m, 1H), 3.98 (s, 8H)

5 1,3-benzothiazol-2-yl(2-[(2-(3-pyridinyl)ethyl]amino)-4-pyrimidinyl)acetonitrile (2 TFA) **38**
(Y = 74%); MS : 373.0 (M+1); HPLC (Conditions a, 263 nm) : 99%, rt. 2.92 min

10 ¹H NMR (DMSO-*d*6) δ 8.81 (d, *J* = 1.13 Hz, 1H), 8.71 (dd, *J* = 5.27 Hz, *J* = 1.13 Hz, 1H), 8.31 (d, *J* = 7.91 Hz, 1H),
7.94 (br s, 1H), 7.85-7.73 (m, 3H), 7.60 (br d, 1H), 7.45-7.40 (m, 1H), 7.29-7.24 (m, 1H), 6.43 (d, *J* = 7.14 Hz, 1H),
6.00-4.40 (m, 2H), 4.05-3.87 (m, 2H), 3.19-3.15 (m, 2H)

15 1,3-benzothiazol-2-yl(5-bromo-2-[(2-(dimethylamino)ethyl]amino)-4-pyrimidinyl)acetonitrile **39**
(Y = 2%); MS : 419.0 (M+1); HPLC (Conditions a, 285 nm) : 88%, rt. 8.00 min

10 ¹H NMR (DMSO-*d*6) δ 11.30 (v br s, 1H, exchangeable), 7.76 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.26-7.21 (m, 1H), 7.04-6.99 (m, 1H), 6.55 (br s, 1H), 3.75-3.45 (m, 2H), 3.15-2.95 (m, 2H), 2.64 (s, 6H).

Example 3 : Preparation of 1,3-benzothiazol-2-yl(2-methoxy-4-pyrimidinyl)-acetonitrile **40**

15 [0096] To a suspension of 1 (0.1g, 0.35 mmol) in dry MeOH (3 ml) was added MeONa (0.08 g, 1.4 mmol) and Et₃N (0.05ml, 0.35 mmol) and the suspension was warmed up to 60°C for 6 days. The solid present was filtered off and the filtrate concentrated to near dryness. The solid residue obtained was washed with water until neutral pH, then dried under vacuum at 40°C to afford 44 mg (45%) of the title compound as a yellow powder.: mp 234 °C dec., MS : 283 (M+1); HPLC (Conditions a, 262 nm) : 97%, rt. 3.40 min;

20 ¹H NMR (DMSO-*d*6) δ 7.79 (d, *J* = 4.52 Hz, 1H), 7.78 (d, *J* = 7.91 Hz, 1H), 7.55 (d, *J* = 7.91 Hz, 1H), 7.29-7.23 (m, 1H),
7.07-7.02 (m, 1H), 6.53 (br d, 1H), 4.02 (s, 3H)

25 [0097] Upon using the procedure described above in the example 3 and the appropriate starting material and reagents, the following additional benzothiazole derivatives of formula III could be obtained.

Example 4 : Preparation of (2-chloro-4-pyrimidinyl)(3-methyl-1,3-benzothiazol-2(3H)-ylidene)ethanenitrile **41**

30 [0098] To a solution of 1 (0.1g, 0.35 mmol) in dry DMSO was added dry K₂CO₃ then methyl iodide and the suspension was shaken at rt. for 2 days. The precipitate formed by addition of water was filtered off then washed with water until neutral pH. The crude residue, dried under vacuum at 40°C, was triturated in warm acetonitrile, filtered off then dried under vacuum at 40°C, affording 5.6 mg (5%) of the title compound as a yellow powder.

35 MS 623 (2M+Na); HPLC (Conditions a, 388 nm) 99%, rt. 5.31 min

1H NMR (DMSO-*d*6) δ 8.01 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.4 Hz, 1H), 7.45-7.40 (m, 1H),
7.31-7.24 (m, 1H), 6.81 (d, *J* = 7.4 Hz, 1H), 3.67 (s, 3H)

Example 5 : Preparation of a pharmaceutical formulation

40 [0099] The following formulation examples illustrate representative pharmaceutical compositions according to the present invention being not restricted thereto.

Formulation 1 - Tablets

45 [0100] A benzazole compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ration. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg of active benzazole compound per tablet) in a tablet press.

Formulation 2 - Capsules

50 [0101] A benzazole compound of formula I is admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active benzazole compound per capsule).

Formulation 3 - Liquid

55 [0102] A benzazole compound of formula I (1250 mg), sucrose (1.75 g) and xanthan gum (4 mg) are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously prepared solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water is then added to produce a total volume of 5 mL.

Formulation 4 - Tablets

5 [0103] A benzazole compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active benzazole compound) in a tablet press.

Formulation 5 - Injection

10 [0104] A benzazole compound of formula I is dissolved in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/ml.

Example 6 : Biological assays

15 [0105] **JNK2 and 3 In vitro assays:** JNK3 and/or 2 assays are performed in 96 well MTT plates, by incubation of 0.5 µg of recombinant, pre-activated GST-JNK3 with 1 µg of recombinant, biotinylated GST-c-Jun and 2 µM $^{33}\gamma$ -ATP (2 nCi/µl), in the presence or absence of benzazole inhibitors and in a reaction volume of 50 µl containing 50 mM Tris-HCl, pH 8.0; 10 mM MgCl₂; 1 mM Dithiothreitol, and 100 µM NaVO₄. The incubation is performed for 120 min. at R.T and stopped upon addition of 200 µl of a solution containing 250 µg of Streptavidine-coated SPA beads (Amersham, Inc.)*, 5 mM EDTA, 0.1% Triton X-100 and 50 µM ATP, in phosphate saline buffer. After incubation for 60 minutes at 20 RT, beads are sedimented by centrifugation at 1500 x g for 5 minutes, resuspended in 200 µl of PBS containing 5 mM EDTA, 0.1% Triton X-100 and 50 µM ATP and the radioactivity measured in a scintillation β counter, following sedimentation of the beads as described above. By substituting GST-c Jun for biotinylated GST-1,ATF₂ or myelin basic protein, this assay can be used to measure inhibition of preactivated p38 and ERK MAP Kinases, respectively.

25 [0106] **Sympathetic Neuron Culture and Survival Assay :** Sympathetic neurons from superior cervical ganglia (SCG) of newborn rats (p4) are dissociated in dispase, plated at a density of 10⁴ cells/cm² in 48 well MTT plates coated with rat tail collagen, and cultured in Leibowitz medium containing 5% rat serum, 0.75 µg/ml NGF 7S (Boehringer Mannheim Corp., Indianapolis, IN.) and arabinosine 10⁻⁵M. Cell death is induced at day 4 after plating by exposing the culture to medium containing 10 µg/ml of anti NGF anti-body (Boehringer Mannheim Corp., Indianapolis, IN.) and no NGF or arabinosine, in the presence or absence of benzazole inhibitors. 24 hours after cell death induction, determination of cell viability is performed by incubation of the culture for 1 hour, at 37°C in 0.5 mg/ml of 3-(4,5-dimethylthiazol-2-yl)2,5 diphenyl tetrazolium bromide (MTT). After incubation in MTT cells are resuspended in DMSO, transferred to a 96 MTT plate and cell viability is evaluated by measuring optical density at 590 nm.

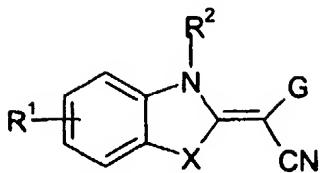
Biological Results

35 [0107] The activities of the benzazole derivatives claimed in the formula I were assessed using the above described in vitro and in vivo biological assays. Representative values are given in the table shown below:

Compound	JNK3	JNK2	p38	ERK2
1	290	500	>30000	>30000
5	400	1200	>30000	>30000
15	70	210	>30000	>30000
20	950	2300	>30000	>30000
28	960	1800	>30000	>30000
40	105	450	>30000	>30000

40 [0108] The values indicated in respect of JNK2 and 3, p38 and ERK2 refer to the IC₅₀ (nM), i.e. the amount necessary to achieve 50% inhibition of said target (e.g. JNK2 or 3). AS# denotes an exemplary test compound as set out with its number in the above examples. From the above table it could be derived that said test compounds according to formula I do have a significant effect both on JNK2 and more notably on JNK 3, but virtually no effect onto p38 and ERK2, thus delivering a quite selective inhibitory effect.

55 Claims**1. Benzazole derivatives according to formula I**



as well as its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof, wherein

15

X is O, S or NR⁰, with R⁰ being H or an unsubstituted or substituted C₁-C₆ alkyl;

20

G is selected from the group comprising or consisting of unsubstituted or substituted aryl or heteroaryl substituents, unsubstituted or substituted 3-8-membered saturated or unsaturated ring systems containing at least one heteroatom selected from N, O or S; said 3-8-membered ring system may be fused with a substituted or unsubstituted aryl or heteroaryl system thus providing a bicyclic system;

25

R¹ is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C₁-C₆-alkoxy, unsubstituted or substituted C₁-C₆-thioalkoxy, unsubstituted or substituted C₁-C₆-alkyl, unsubstituted or substituted C₂-C₆-alkenyl, unsubstituted or substituted C₂-C₆-alkynyl, primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, unsubstituted or substituted C₁-C₆ alkoxy carbonyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxyl, sulfonyl, sulfonamide, unsubstituted or substituted hydrazides;

30

R² is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C₁-C₆-alkyl, unsubstituted or substituted C₂-C₆-alkenyl, unsubstituted or substituted C₂-C₆-alkynyl, unsubstituted or substituted C₁-C₆-alkyl-aryl, unsubstituted or substituted aryl or heteroaryl, unsubstituted or substituted C₁-C₆-alkyl-heteroaryl, -C(O)-OR³, -C(O)-R³, -C(O)-NR³R³, -(SO₂)R³, with

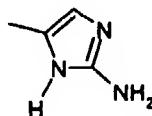
35

R³ and R³ being independently selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted C₁-C₆-alkyl aryl, unsubstituted or substituted C₁-C₆-alkyl heteroaryl,

40

with the proviso that if X is S or NH, while R¹ and R² are both H, G shall not be

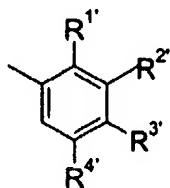
45



with the further proviso that if X is S, R¹ and R² are both H, G shall not be

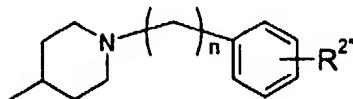
50

55



with R¹ being H, methyl or —OCH₃, R² and R³ being H or methyl and R⁴ being H, methyl or —OCH₃, with the further proviso that if X is S or O, R¹ and R² are both H, G shall not be

5

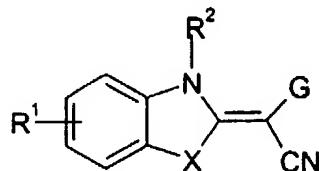


10

with R² being H, lower alkyl, lower alkoxy or halogen and with n = 1-4, with the final proviso that if X is O, S or NR, with R being H, C₁-C₄ alkyl or aryl, G shall not be a 4-diazo-, or 4-diazoniumphenyl group.

15 2. Benzazole derivatives according to formula I

20



25

I

as well as its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof, wherein

30

X is O, S or NR⁰, with R⁰ being H or an unsubstituted or substituted C₁-C₆ alkyl;

35

G is selected from the group comprising or consisting of unsubstituted or substituted aryl or heteroaryl substituents, unsubstituted or substituted 3-8-membered saturated or unsaturated ring systems containing at least one heteroatom selected from N, O or S; said 3-8-membered ring system may be fused with a substituted or unsubstituted aryl or heteroaryl system thus providing a bicyclic system;

40

R¹ is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C₁-C₆-alkoxy, unsubstituted or substituted C₁-C₆-thioalkoxy, unsubstituted or substituted C₁-C₆-alkyl, unsubstituted or substituted C₂-C₆-alkenyl, unsubstituted or substituted C₂-C₆-alkynyl, primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, unsubstituted or substituted C₁-C₆ alkoxycarbonyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, sulfonyl, sulfonamide, unsubstituted or substituted hydrazides;

45

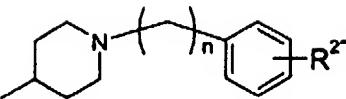
R² is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C₁-C₆-alkyl, unsubstituted or substituted C₂-C₆-alkenyl, unsubstituted or substituted C₂-C₆-alkynyl, unsubstituted or substituted C₁-C₆-alkyl-aryl, unsubstituted or substituted aryl or heteroaryl, unsubstituted or substituted C₁-C₆-alkyl-heteroaryl, -C(O)-OR³, -C(O)-R³, -C(O)-NR³R³, -(SO₂)R³, with

50

R³ and R³ being independently selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted C₁-C₆-alkyl aryl, unsubstituted or substituted C₁-C₆-alkyl heteroaryl,

55

with the proviso that if X is S or O, R¹ and R² are both H, G shall not be



with R^{2*} being H, lower alkyl, lower alkoxy or halogen and with $n = 1-4$, for use as a medicament.

10 3. A benzazole derivative according to claim 1 or 2, wherein R^2 is hydrogen, an unsubstituted or substituted C_1-C_6 alkyl, an unsubstituted or substituted C_1-C_6 alkylaryl or C_1-C_6 alkyl-heteroaryl group, $-C(O)-R^3$, $-C(O)-NR^3R^3'$, $-(SO_2)R^3$, whereby R^3 and R^3' are as above defined.

15 4. A benzazole derivative according to any of the preceding claims, wherein R^2 is hydrogen and R^1 , X and G are as above defined.

5. A benzazole derivative according to any of the preceding claims, wherein R^1 is selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy.

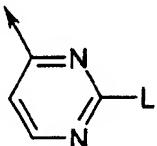
20 6. A benzazole derivative according to claim 4, wherein R^3 and R^3' are selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, C_1-C_6 -alkyl aryl, C_1-C_6 - alkyl heteroaryl.

7. A benzazole derivative according to claim 6, wherein R^3 and R^3' is hydrogen or C_1-C_6 alkyl.

25 8. A benzazole derivative according any of the preceding claims, wherein said aryl or heteroaryl group is substituted with at least one substituent selected from the group consisting of unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 alkoxy, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted alkenyl, amino, aminoacyl, aminocarbonyl, unsubstituted or substituted C_1-C_6 - alkoxycarbonyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxyl, C_1-C_6 alkoxythio.

30 9. A benzazole derivative according to any of the preceding claims, wherein G is an unsubstituted or substituted pyrimidinyl group.

35 10. A benzazole derivative according to claim 9, wherein G is a pyrimidinyl group



45 45. wherein L is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 alkoxy, unsubstituted or substituted C_1-C_6 thioalkoxy, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, amino-(C_1-C_{10})-alkyl, amino- unsubstituted or substituted (C_1-C_{10})-alkyl-aryl, amino- unsubstituted or substituted (C_1-C_{10})-alkylheteroaryl, unsubstituted or substituted C_1-C_6 alkoxycarbonyl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted 3-8 membered cycloalkyl, optionally containing at least one heteroatom selected from N, O, S, and unsubstituted or substituted hydrazido groups.

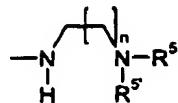
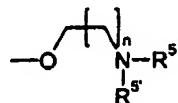
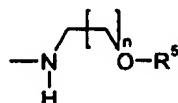
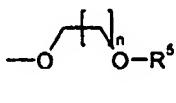
50 55. 11. A benzazole derivative according to claim 10, wherein L is a substituted or unsubstituted (C_1-C_{10})-alkyl group.

12. A benzazole derivative according to claim 10, wherein L is a group $-N(R^a, R^b)$ or $-OR^a$, with R^a and R^b being each independently selected from the group consisting of H, unsubstituted or substituted (C_1-C_{10})-alkyl, unsubstituted or substituted C_1-C_6 alkyl-aryl, unsubstituted or substituted C_1-C_6 -alkyl-heteroaryl, unsubstituted or substituted

aryl or heteroaryl and unsubstituted or substituted 4-8 membered saturated or unsaturated cycloalkyl.

13. A benzazole derivative according to claim 12 wherein L is selected from

5



10

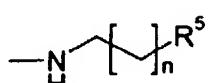
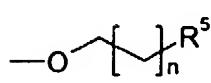
(a)

(b)

(c)

(d)

15



(e)

(f)

wherein n is 1 to 10, preferably 1 to 6

R5 and R5' are independently selected from each other from the group consisting of H, substituted or unsubstituted C1-C10 alkyl, substituted or unsubstituted aryl or heteroaryl, substituted or unsubstituted C1-C6 alkyl-aryl and substituted or unsubstituted C1-C6-alkyl-heteroaryl.

14. A benzazole derivative according to claim 13, wherein R5' is an unsubstituted or substituted imidazolyl.

30 15. A benzazole derivative according to any of the preceding claims, wherein X is S, R1 is H and R2 is H.

16. A benzazole derivative according to any of the preceding claims selected from the following group:

35 1,3-benzothiazol-2-yl(2-chloro-4-pyrimidinyl)-acetonitrile
 1,3-benzothiazol-2-yl(2,6-dimethoxy-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl[3-chloro-5-(trifluoromethyl)-2-pyridinyl]acetonitrile
 1,3-benzothiazol-2-yl(2-chloro-6-methyl-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl[2-(methylsulfanyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl(6-chloro-5-nitro-4-pyrimidinyl)acetonitrile
 40 1,3-benzothiazol-2-yl(2-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-oxo-2,3-dihydro-4-pyridinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-phenyl-4-quinazolinyl)acetonitrile
 (6-chloro-1,3-benzothiazol-2-yl)(phenyl)acetonitrile
 1,3-benzothiazol-2-yl(5-chloro-2-pyridinyl)acetonitrile
 45 1,3-benzothiazol-2-yl(phenyl)acetonitrile
 1,3-benzothiazol-2-yl(6-chloro-2-pyridinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-pyrazinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-[(2-(1H-imidazol-4-yl)ethyl]amino)-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl[2-(1-piperazinyl)-4-pyrimidinyl]acetonitrile
 50 1,3-benzothiazol-2-yl[2-(4-benzyl-1-piperidinyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(4-methyl-1-piperazinyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(4-morpholinyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(methylamino)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(4-[2-(4-morpholinyl)ethyl]-1-piperazinyl)-4-pyrimidinyl]acetonitrile
 55 1,3-benzothiazol-2-yl[2-(4-(benzyloxy)-1-piperidinyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(4-hydroxy-1-piperidinyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl(2-hydrazino-4-pyrimidinyl)acetonitrile
 1,3-benzothiazol-2-yl(2-[(2-dimethylamino)ethyl]amino)-4-pyrimidinyl)acetonitrile

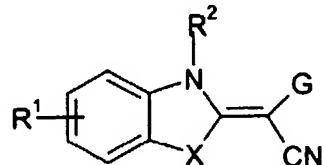
1,3-benzothiazol-2-yl[2-(dimethylamino)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[(2-methoxyethyl)amino]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[(2-hydroxyethyl)amino]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(propylamino)-4-pyrimidinyl]acetonitrile
 5 1,3-benzothiazol-2-yl[2-[(3-(1H-imidazol-1-yl)propyl)amino]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(1-pyrrolidinyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[(2-phenylethyl)amino]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[(2-pyridinyl)ethyl]amino]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[(2-pyridinyl)methyl]amino]-4-pyrimidinyl]acetonitrile
 10 1,3-benzothiazol-2-yl[2-[4-(1H-1,2,3-benzotriazol-1-yl)-1-piperidinyl]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[4-(2-pyrazinyl)-1-piperazinyl]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[4-(2-pyrimidinyl)-1-piperazinyl]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[(2-(3-pyridinyl)ethyl)amino]-4-pyrimidinyl]acetonitrile le
 1,3-benzothiazol-2-yl[2-[(2-(dimethylamino)ethyl)amino]-4-pyrimidinyl]acetonitrile
 15 1,3-benzothiazol-2-yl[2-(2-methoxy-4-pyrimidinyl)-acetonitrile
 (2-chloro-4-pyrimidinyl)(3-methyl-1,3-benzothiazol-2(3H)-ylidene)ethanenitrile
 1,3-benzothiazol-2-yl[2-(methylsulfanyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-chloro-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(methylamino)-4-pyrimidinyl]acetonitrile
 20 1,3-benzothiazol-2-yl[2-[(1H-imidazol-4-yl)ethyl]amino]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[(2-hydroxyethyl)amino]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(2-methoxy-4-pyrimidinyl)acetonitrile

17. A benzazole derivative according to claim 16, which is selected from the group consisting of:

25 1,3-benzothiazol-2-yl[2-(methylsulfanyl)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-chloro-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(methylamino)-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-[(2-(1H-imidazol-4-yl)ethyl)amino]-4-pyrimidinyl]acetonitrile
 30 1,3-benzothiazol-2-yl[2-[(2-hydroxyethyl)amino]-4-pyrimidinyl]acetonitrile
 1,3-benzothiazol-2-yl[2-(2-methoxy-4-pyrimidinyl)acetonitrile

18. Use of a benzazole derivatives according to formula I

35



45

as well as its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof, wherein

50

X is O, S or NR⁰, with R⁰ being H or an unsubstituted or substituted C₁-C₆ alkyl;

55

G is selected from the group comprising or consisting of unsubstituted or substituted aryl or heteroaryl substituents, unsubstituted or substituted 3-8-membered saturated or unsaturated ring systems containing at least one heteroatom selected from N, O or S; said 3-8-membered ring system may be fused with a substituted or unsubstituted aryl or heteroaryl system thus providing a bicyclic system;

R¹ is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C₁-C₆-alkoxy, unsubstituted or substituted C₁-C₆-thioalkoxy, unsubstituted or substituted C₁-C₆-alkyl, unsubstituted or sub-

stituted C_2 - C_6 -alkenyl, unsubstituted or substituted C_2 - C_6 -alkynyl, primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, unsubstituted or substituted C_1 - C_6 alkoxy carbonyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, sulfonyl, sulfonamide, unsubstituted or substituted hydrazides;

5 R^2 is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1 - C_6 -alkyl, unsubstituted or substituted C_2 - C_6 -alkenyl, unsubstituted or substituted C_2 - C_6 -alkynyl, unsubstituted or substituted C_1 - C_6 -alkyl-aryl, unsubstituted or substituted aryl or heteroaryl, unsubstituted or substituted C_1 - C_6 -alkyl-heteroaryl, $C(O)-OR^3$, $-C(O)-R^3$, $-C(O)-NR^3R^3$, $-(SO_2)R^3$, with

10 R^3 and R^3 being independently selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1 - C_6 alkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted C_1 - C_6 -alkyl aryl, unsubstituted or substituted C_1 - C_6 -alkyl heteroaryl,

15 for the preparation of a pharmaceutical composition for the modulation of the JNK pathway.

19. Use according to claim 18 for the treatment or prevention of disorders associated with the abnormal expression or activity of JNK.

20. Use according to claim 19 for the treatment or prevention of disorders associated with the abnormal expression or activity of JNK2 and/or 3.

21. Use according to any of claims 19 to 20 for the treatment of neuronal disorders including epilepsy; Alzheimer's disease, Parkinson's disease, retinal disease, spinal cord injury, head trauma.

25. Use according to any of claims 19 to 20 for the treatment of autoimmune diseases including Multiple Sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis, asthma, septic shock, transplant rejection.

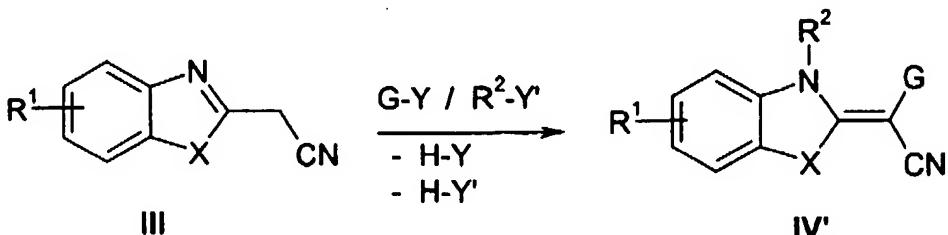
30. Use according to any of claims 19 to 20 for the treatment of cancer including breast-, colorectal, pancreatic cancer.

35. Use according to any of claims 19 to 20 for the treatment of cardiovascular diseases including stroke, arterosclerosis, myocardial infarction, myocardial reperfusion injury.

40. 25. A pharmaceutical composition containing at least one benzazole derivative according to any of the claims 2 to 17 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

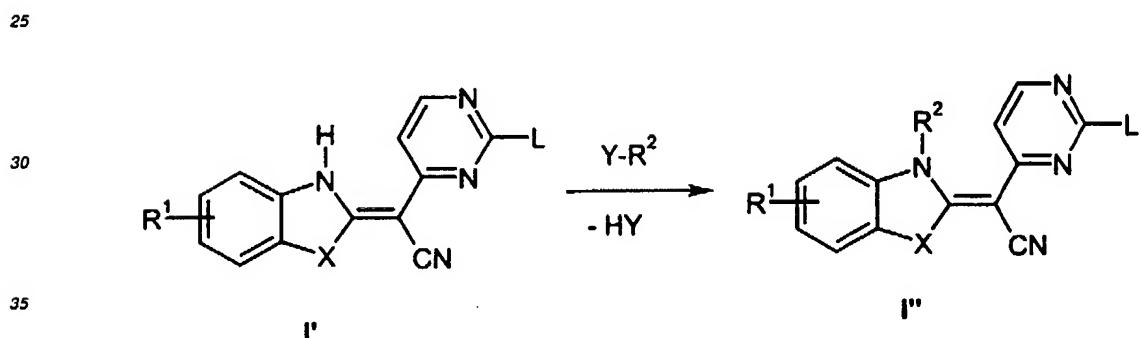
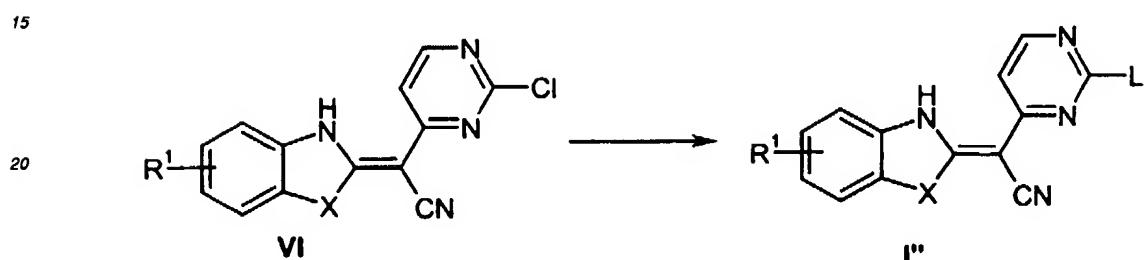
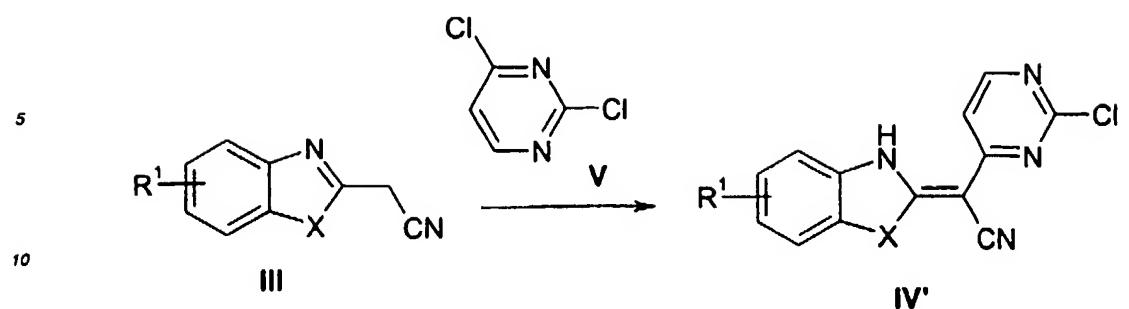
45. 26. Process for the preparation of a benzazole derivative according to any of claims 1 to 17, wherein the following reaction is performed :

40



50 whereby X and G are as above described and Y, Y' are suitable leaving groups like halogen.

55. 27. Process according to claim 26, wherein the following reactions are performed :



with R¹, R², Y and X being as described above.

40

45

50

55



DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	BIEHL E R ET AL: "LDA (lithium diisopropylamide) mediated reactions of 1-naphthalynes with lithiated acetonitriles and 1,4-dipolar nucleophilic anions" SYNTHESIS, no. 9, September 1993 (1993-09), pages 885-888, XP002138990 * page 886, compounds 13, 14 * ---	1,3-8,26	C07D277/64 C07D263/56 C07D235/16 C07D417/06 C07D417/14 C07D413/06 C07D403/06 A61K31/4184 A61K31/428 A61K31/423
X	US 2 918 369 A (DOORENBOS N J ET AL) 22 December 1959 (1959-12-22) * example XIII *---	1,3-8,15	A61P25/00
X	DE 26 17 345 A (FUJI PHOTO FILM CO., LTD.) 4 November 1976 (1976-11-04) * examples 26,34 *---	1,3-8	
X	HUNGER A ET AL: "Benzimidazol-Derivate und verwandte Heterocyclen VI) Synthese von Pheny-'1-aminoalkyl-benzimidazolyl-(2)!-essigsäure-estern und amiden" HELVETICA CHIMICA ACTA, vol. 43, no. 6, 17 October 1960 (1960-10-17), pages 1727-1733, XP002138991 * page 1728, compounds III and VI, page 1730, table 2 *---	1,3-8	
X	EP 0 364 765 A (BAYER AG) 25 April 1990 (1990-04-25) * pages 18-20, 32, 33 *---	1,3-8,15 -/-	
The present search report has been drawn up for all claims			
Place of search THE HAGUE	Date of completion of the search 30 May 2000	Examiner Allard, M	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant & taken alone Y : particularly relevant & combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 81 1207

DOCUMENTS CONSIDERED TO BE RELEVANT									
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)						
X	HUANG Z T ET AL: "Synthesis, reactions, and tautomerism of ketene N,S-acetals with benzothiazoline ring" CHEMISCHE BERICHTE, vol. 123, no. 3, March 1990 (1990-03), pages 541-547, XP002138992 * page 545, compound 3h *	1,3-8, 15, 16							
X	CHEMICAL ABSTRACTS, vol. 117, no. 23, 7 December 1992 (1992-12-07) Columbus, Ohio, US; abstract no. 233799s, VOLOVENKO Y M ET AL: "Synthesis and biological activity of alpha-substituted 2-pyridylacetonitriles" page 850; XP002138993 * abstract * & UKR. KHIM. ZH. (RUSS. ED.), vol. 58, no. 5, 1992, pages 430-432,	1-8, 15							
X	DATABASE CROSSFIRE 'Online! Beilstein Institut fuer Literatur der organischen Chemie XP002138996 * Beilstein Registry Number 1128326 * & JUSTUS LIEBIGS ANN. CHEM., 1978, pages 473-511,	1,3-8	TECHNICAL FIELDS SEARCHED (Int.Cl.7)						
X	DATABASE CROSSFIRE 'Online! Beilstein Institut fuer Literatur der organischen Chemie XP002138997 * Beilstein Registry Number 5395626, 5395012, 5395000 and 5392953 * & ZH. ORG. KHIM., vol. 1, 1965, pages 756-762.	1,3-8, 15							
			-/--						
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 33%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>30 May 2000</td> <td>Allard, M</td> </tr> </table> <p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>				Place of search	Date of completion of the search	Examiner	THE HAGUE	30 May 2000	Allard, M
Place of search	Date of completion of the search	Examiner							
THE HAGUE	30 May 2000	Allard, M							



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 81 1207

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	<p>DATABASE CROSSFIRE 'Online! Beilstein Institut fuer Literatur der organischen Chemie XP002138998 * Beilstein Registry Number 5589714, 5589715, 5589716, 5589718, 5589719, 5589720, 5589721, 5589722, 5589723 and 5601864 *</p> <p>& J. PRAKT. CHEM., vol. 324, no. 1, 1982, pages 3-11,</p> <p>---</p>	1,3-8,15	
X	<p>DATABASE CROSSFIRE 'Online! Beilstein Institut fuer Literatur der organischen Chemie XP002138999 * Beilstein Registry Number 855092, 861654 and 874268 *</p> <p>& ZH. ORG. KHIM., vol. 15, 1979, page 200</p> <p>---</p>	1,3-8	
X	<p>DATABASE CROSSFIRE 'Online! Beilstein Institut fuer Literatur der organischen Chemie XP002139000 * Beilstein Registry Numbers 3616387 and 3614951 *</p> <p>& HETEROCYCLES, vol. 31, no. 6, 1990, pages 1115-1127.</p> <p>---</p>	1,3-8	TECHNICAL FIELDS SEARCHED (Int.Cl.)
X	<p>DATABASE CROSSFIRE 'Online! Beilstein Institut fuer Literatur der organischen Chemie XP002139001 * Beilstein Registry Number 6226072, 6220826, 6220828, 6235458, 6231468 and 6231469 *</p> <p>& J. PRAKT. CHEM., vol. 330, no. 4, 1988, pages 590-606.</p> <p>---</p> <p>-/-</p>	1,3-8,15	
<p>The present search report has been drawn up for all claims</p>			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	30 May 2000	Allard, M	
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			



DOCUMENTS CONSIDERED TO BE RELEVANT									
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)						
X	<p>DATABASE CROSSFIRE 'Online! Beilstein Institut fuer Literatur der organischen Chemie XP002139002 * Beilstein Registry Number 5115381, 5130108, 5161287 and 5169755 * & KHIM. GETEROTSIKL. SOEDIN., vol. 8, 1988, pages 1119-1123, ---</p>	1,3-8							
D,X	<p>DATABASE WPI Section Ch, Week 199923 Derwent Publications Ltd., London, GB; Class B02, AN 1999-266986 XP002139004 -& JP 11 080155 A (TOA FOOD CHEM CO LTD), 26 March 1999 (1999-03-26) * abstract *---</p>	18-20,24							
X	<p>CHEMICAL ABSTRACTS, vol. 126, no. 6, 10 February 1997 (1997-02-10) Columbus, Ohio, US; abstract no. 74791a, HASSAN A A ET AL: "Reaction of benzimidazolylacetonitrile and -methanethiol with electron deficient compounds" page 583; XP002138994 * abstract * -& CHEMICAL ABSTRACTS, vol. 126, no. 1. 1 January 1997 (1997-01-01) Columbus, Ohio, US; FORMULA INDEX: page 1990F; XP002138995 * Compound with formula C15H8C13N3O2 * & HETEROCYCL. COMMUN., vol. 2, no. 5, 1996, pages 441-446, ---</p>	1,3-8	<p>TECHNICAL FIELDS SEARCHED (Int.Cl.7)</p>						
<p>The present search report has been drawn up for all claims</p> <table border="1"> <tr> <th>Place of search</th> <th>Date of completion of the search</th> <th>Examiner</th> </tr> <tr> <td>THE HAGUE</td> <td>30 May 2000</td> <td>Allard, M</td> </tr> </table> <p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on or after the filing date D : document cited in the application L : document cited for other reasons & member of the same patent family, corresponding document</p>				Place of search	Date of completion of the search	Examiner	THE HAGUE	30 May 2000	Allard, M
Place of search	Date of completion of the search	Examiner							
THE HAGUE	30 May 2000	Allard, M							



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 99 81 1207

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D, X	<p>DATABASE CHEMICAL ABSTRACTS 'Online! Chemical Abstracts Services, Columbus, Ohio, US AN 117-233221: XP002139003 * Registry Number 144061-99-4, 144061-98-3, 144061-97-2, 144061-96-1, 144061-95-0 and 92498-43-6 *</p> <p>& HETEROCYCLES, vol. 34, no. 6, 1992, pages 1239-1249.</p> <p>---</p>	1,3-8	
A	<p>WO 99 21859 A (GLAXO GROUP LIMITED) 6 May 1999 (1999-05-06) * claims 1,25,26 *</p> <p>---</p>	1,18	
A	<p>MARONEY A C ET AL: "Motoneuron apoptosis is blocked by CEP-1347 (KT 7515), a novel inhibitor of the JNK signaling pathway" JOURNAL OF NEUROSCIENCE, vol. 18, no. 1, 1 January 1998 (1998-01-01), pages 104-111-111, XP000870100 ISSN: 0270-6474 * the whole document *</p> <p>-----</p>	1,18	
TECHNICAL FIELDS SEARCHED (Int.Cl.7)			

The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	30 May 2000	Allard, M	
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>	
<p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p>			

ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.

EP 99 81 1207

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

30-05-2000

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 2918369	A	22-12-1959	NONE		
DE 2617345	A	04-11-1976	JP 51123223 A	27-10-1976	
			GB 1541936 A	14-03-1979	
EP 364765	A	25-04-1990	AU 617537 B	28-11-1991	
			AU 4246289 A	21-06-1990	
			BR 8905104 A	15-05-1990	
			CA 2000234 A	08-04-1990	
			CS 8905679 A	12-09-1990	
			DD 288380 A	28-03-1991	
			DK 494589 A	09-04-1990	
			HU 54358 A,B	28-02-1991	
			JP 2164873 A	25-06-1990	
			NZ 230925 A	26-07-1991	
			US 4933341 A	12-06-1990	
			US 5196562 A	23-03-1993	
			ZA 8907614 A	24-12-1991	
JP 11080155	A	26-03-1999	NONE		
WO 9921859	A	06-05-1999	AU 1151099 A	17-05-1999	

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82